Clinical trial results:
A randomized double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2008-008698-69
Trial protocol	IT CZ NL FR BE GB DE SE ES HU AT
Global end of trial date	04 December 2014
Results information	
Result version number	v1 (current)
This version publication date	18 July 2018
First version publication date	18 July 2018

Trial information

Trial identification	
Sponsor protocol code	CRAD001Y2301
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00863655
WHO universal trial number (UTN)	-

Notes:

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

Notes:

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the combination treatment of everolimus and exemestane to exemestane alone with respect to progression-free survival (PFS) in postmenopausal women with ERpositive breast cancer that is refractory to NSAIs

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	03 June 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 43
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	Egypt: 6
Country: Number of subjects enrolled	France: 51
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Japan: 106
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Netherlands: 18

Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Thailand: 18
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United States: 223
Worldwide total number of subjects	724
EEA total number of subjects	278

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)	449
From 65 to 84 years	263
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Although 724 patients were randomized, 4 never received any study treatment and thus were excluded form the safety set.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus + Exemestane

Arm description:

Everolimus 10 mg daily in combination with exemestane 25 mg 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:

10-mg oral daily dosing regimen (two 5-mg tablets)

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

Dosage and administration details:

25 mg orally daily

Arm title	Placebo + Exemestane

Arm description:

Placebo of everolimus in combination with exemestane 25 mg daily

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

Dosage and administration details:

oral daily dosing of two 5-mg tablets. Placebo was formulated to be indistinguishable from the everolimus tablets.

Number of subjects in period 1	Everolimus + Exemestane	Placebo + Exemestane
Started	485	239
Completed	0	0
Not completed	485	239
Adverse event, serious fatal	7	1
Consent withdrawn by subject	47	7
Disease progression	364	221
Treatment completed as per protocol	5	1
Adverse event, non-fatal	52	8
New cancer therapy	5	1
Administrative problems	1	-
Protocol deviation	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus + Exemestane
Reporting group description:	
Everolimus 10 mg daily in combination with exemestane 25 mg daily	
Reporting group title	Placebo + Exemestane
Reporting group description:	
Placebo of everolimus in combination with exemestane 25 mg daily	

Reporting group values	Everolimus + Exemestane	Placebo + Exemestane	Total
Number of subjects	485	239	724
Age, Customized Units: Participants			
< 65 years	290	159	449
>= 65 years	195	80	275
Age Continuous Units: years			
arithmetic mean	62.5	61.2	
standard deviation	± 10.31	± 9.75	-
Gender, Male/Female Units: participants			
Female	485	239	724
Male	0	0	0

End points

End points reporting groups

Reporting group title	Everolimus + Exemestane
Reporting group description:	
Everolimus 10 mg daily in combination with exemestane 25 mg daily	
Reporting group title	Placebo + Exemestane
Reporting group description:	
Placebo of everolimus in combination with exemestane 25 mg daily	

Primary: Progression-free survival (PFS) based on local radiology review of tumor assessments.

End point title	Progression-free survival (PFS) based on local radiology review of tumor assessments.

End point description:

Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST 1.0). For patients with no target lesion, in the absence of new lesions, the overall lesion response at each assessment was one of following: Complete Response CR), Stable Disease SD), Unknown, or Progressive Disease (PD) based on non-target lesion responses. The following is considered progression among patients with lytic or mixed (lytic+sclerotic) bone lesions: appearance of ≥1 new lytic lesions in bone; the appearance of ≥ new lesions outside of bone and unequivocal progression of existing bone lesions.

End point type	Primary

End point timeframe:

date of randomization to the date of first documented tumor progression or death from any cause, whichever occurs first ,reported between day of first patient randomized, 27 July 2009, until cut-off date 11 February 2011.

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	239		
Units: months				
median (confidence interval 95%)	6.93 (6.44 to 8.05)	2.83 (2.76 to 4.14)		

Statistical analyses

Statistical analysis title	Progression free survival analysis
Comparison groups	Everolimus + Exemestane v Placebo + Exemestane
Number of subjects included in analysis	724
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.54

Secondary: Overall survival (OS) by number of deaths

End point title	Overall survival (OS) by number of deaths

End point description:

Overall survival, the key secondary endpoint in this study, is defined as the time from date of randomization to the date of death due to any cause. If a patient is not known to have died, survival was censored at the date of last contact.

End point type	Secondary

End point timeframe:

up to 53 months

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	239		
Units: Participants	267	143		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) by median

End point title	Overall survival (OS) by median

End point description:

Overall survival, the key secondary endpoint in this study, is defined as the time from date of randomization to the date of death due to any cause.

End point type	Secondary

End point timeframe:

up to 53 months

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	239		
Units: Months				
median (confidence interval 95%)	30.98 (27.96 to 34.56)	26.55 (22.57 to 33.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)

End point description:

Overall response rate (ORR) is the percentage of patients with a best overall response of complete response (CR) or partial response (PR) according to RECIST 1.0.

End point type	Secondary

End point timeframe:

up to 21 months

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	239		
Units: Percentage of participants				
number (not applicable)	9.5	0.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate (CBR)

End point title	Clinical benefit rate (CBR)

End point description:

CBR is defined as the percentage of patients with best overall response of either complete response (CR), a partial response (PR) or stable disease (SD) >= 24 weeks, according to RECIST 1.0.

End point type	Secondary

End point timeframe:

up to 21 months

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	239		
Units: Percentage of participants				
number (not applicable)	33.4	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration of Eastern Cooperative Oncology Group performance status (ECOG PS) using Kaplan-Meier

End point title	Time to deterioration of Eastern Cooperative Oncology Group performance status (ECOG PS) using Kaplan-Meier

End point description:

ECOG PS scale was used to assess physical health of patients. The ECOG performance status Scale Index allows patients to be classified. ECOG scale index: 0 - Fully active, able to carry on all pre-disease performance without restriction. 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. 3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. 5 - Dead

End point type	Secondary

End point timeframe:

2, 4, 6, 9 months

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	239		
Units: Percentage of participants				
median (confidence interval 95%)				
2 Months	0.84 (0.8 to 0.87)	0.87 (0.82 to 0.91)		
4 Months	0.74 (0.7 to 0.78)	0.8 (0.73 to 0.85)		
6 Months	0.64 (0.58 to 0.69)	0.67 (0.57 to 0.75)		
9 Months	0.57 (0.5 to 0.63)	0.47 (0.32 to 0.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported outcomes (PROs): Time to deterioration of PRO scores using Kaplan Meier: EORTC QLQ-C30

End point title	Patient-reported outcomes (PROs): Time to deterioration of PRO scores using Kaplan Meier: EORTC QLQ-C30

End point description:

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales, 3 symptom scales, a global health status - QoL scale, and 6 single items. Each of the multi-item scales includes a different set of items - no item occurs in more than 1 scale. All of the scales measures range in score from 0 to 100. A high scale score = higher response level. Thus a high score for a functional scale represents a healthy level of function, a high score for the global health status / QoL represents a high quality of life but a high score for a symptom scale / item represents a high level of symptomatology / problems. The principle for scoring these scales: 1.) Estimate the average of the items that contribute to the scale = raw score. 2.) Linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

End point type	Secondary

End point timeframe:

Up to 21 months

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	239		
Units: Percentage of participants				
median (confidence interval 95%)				
Deterioration global health status score ≥ 5%	4.53 (4.17 to 5.68)	4.4 (3.58 to 5.85)		
Deterioration in PF domain score of ≥ 5%	4.83 (4.17 to 6.97)	4.37 (2.83 to 7)		
Deterioration in EF domain score of ≥ 5%	6.93 (5.55 to 8.41)	6.93 (4.17 to 7.36)		
Deterioration in SF domain score of ≥ 5%	8.34 (6.93 to 10.87)	7.03 (5.62 to 9999.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Overall response based on Investigator per Kaplan Meier

End point title	Time to Overall response based on Investigator per Kaplan Meier

End point description:

overall response = complete response (CR) + partial response (PR) per RECIST 1.0 Time to overall response (CR or PR) based on investigator is the time between date of randomization/start of treatment until first documented response (CR or PR). This analysis included all patients/responders. Patients who did not achieve a confirmed PR or CR were censored at last adequate tumor assessment date when they did not progress (including deaths not due to underlying disease) or at maximum follow-up (i.e. FPFV to LPLV used for the analysis) when they had an event for progression-free survival.

End point type	Secondary

End point timeframe:

2, 4, 6, 9 months

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	239		
Units: Months				
arithmetic mean (confidence interval 95%)				
2 months	0.96 (0.94 to 0.98)	1 (0.97 to 1)		
4 months	0.93 (0.91 to 0.95)	1 (0.97 to 1)		
6 months	0.92 (0.89 to 0.94)	1 (0.97 to 1)		
9 months	0.9 (0.88 to 0.93)	1 (0.97 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of overall response based on Investigator

End point title	Duration of overall response based on Investigator

End point description:

Duration of overall response (CR or PR) based on investigator applies only to patients whose best overall response was CR or PR (RECIST 1.0). The start date was the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

End point type	Secondary

End point timeframe:

up to 21 months

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	485	239		
Units: Months				
median (confidence interval 95%)	8.21 (5.55 to 99999.99)	9999.99 (-99999.99 to 99999.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Everolimus Concentrations at Week 4

End point title	Everolimus Concentrations at Week 4[1]

End point description:

Characterize the pharmacokinetics (PK) of everolimus in combination with exemestane using Cmin (pre-dose) and C2h (post-dose) at week 4 in a small group of patients.

End point type	Secondary

End point timeframe:

pre-dose, 2 hours post-dose

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistics was not done for this endpoint or on the placebo arm.

End point values	Everolimus + Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dose (Cmin) (n:22)	16.04 (± 9.356)			
2 hours post-dose (C2h) (n:24)	46.5 (± 17.954)			

Statistical analyses

No statistical analyses for this end point

Secondary: Exemestane concentrations at week 4

End point title	Exemestane concentrations at week 4

End point description:

Characterize the PK of exemestane in combination with or without everolimus using Cmin and C2h at week 4 in a small group of patients.

End point type	Secondary

End point timeframe:

predose, 2 hours post-dose

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	22		
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dose (Cmin) (n: 34, n: 22)	0.63 (± 0.474)	0.43 (± 0.376)		
2 hours post-dose (C2h) (n: 39, n: 22)	23.16 (± 19.805)	13.3 (± 11.889)		

Statistical analyses

No statistical analyses for this end point

Secondary: Estradiol plasma concentrations

End point title	Estradiol plasma concentrations

End point description:

Compare estradiol concentrations from baseline to week 4 in both treatment arms.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Everolimus + Exemestane	Placebo + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	15		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline (n: 41, 14)	5.62 (± 3.342)	4.09 (± 1.792)		
Week 4 (n: 38, 15)	3.5 (± 2.551)	5.17 (± 6.919)		

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	Placebo + exemestane

Reporting group description:

Placebo + exemestane

Reporting group title	Everolimus 10mg + exemestane

Reporting group description:

Everolimus 10mg + exemestane

Serious adverse events	Placebo + exemestane	Everolimus 10mg + exemestane	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 238 (15.55%)	158 / 482 (32.78%)	
number of deaths (all causes)	4	22	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			

subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to eye			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tumour pain			

subjects affected / exposed	1 / 238 (0.42%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 238 (0.00%)	4 / 482 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Preventive surgery			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 238 (0.00%)	6 / 482 (1.24%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 238 (0.42%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 238 (0.00%)	6 / 482 (1.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyperpyrexia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 238 (0.42%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 238 (0.42%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 238 (1.68%)	7 / 482 (1.45%)	
occurrences causally related to treatment / all	0 / 4	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 238 (0.42%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 238 (0.84%)	12 / 482 (2.49%)	
occurrences causally related to treatment / all	0 / 2	4 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea exertional			
subjects affected / exposed	1 / 238 (0.42%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 238 (0.00%)	5 / 482 (1.04%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal inflammation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 238 (0.42%)	6 / 482 (1.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 238 (0.00%)	13 / 482 (2.70%)	
occurrences causally related to treatment / all	0 / 0	14 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 238 (0.42%)	8 / 482 (1.66%)	
occurrences causally related to treatment / all	0 / 1	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 238 (0.42%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	1 / 238 (0.42%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Fractured sacrum			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	3 / 238 (1.26%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary radiation injury			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subdural haematoma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
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	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			

subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
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 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersomnia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			

subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory disturbance			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tremor			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
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	2 / 238 (0.84%)	8 / 482 (1.66%)	
occurrences causally related to treatment / all	0 / 2	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 238 (0.42%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Diplopia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery thrombosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
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 / 238 (0.00%)	1 / 482 (0.21%)	
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	0 / 238 (0.00%)	6 / 482 (1.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 238 (0.42%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	0 / 238 (0.00%)	4 / 482 (0.83%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 238 (0.42%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			

subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
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 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 238 (0.84%)	5 / 482 (1.04%)	
occurrences causally related to treatment / all	0 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine ulcer			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 238 (1.26%)	6 / 482 (1.24%)	
occurrences causally related to treatment / all	0 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blister			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			

subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder disorder			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 238 (0.00%)	5 / 482 (1.04%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure acute			

subjects affected / exposed	0 / 238 (0.00%)	4 / 482 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 238 (0.84%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			

subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (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	2 / 238 (0.84%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	2 / 238 (0.84%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			

subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 238 (0.42%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			

subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histoplasmosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 238 (0.42%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 238 (0.42%)	11 / 482 (2.28%)	
occurrences causally related to treatment / all	0 / 1	3 / 11	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pneumonia bacterial			
subjects affected / exposed	1 / 238 (0.42%)	0 / 482 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyometra			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
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	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			

subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 238 (0.00%)	3 / 482 (0.62%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 238 (0.42%)	4 / 482 (0.83%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 238 (0.00%)	5 / 482 (1.04%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 238 (0.00%)	2 / 482 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 482 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + exemestane	Everolimus 10mg + exemestane	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	209 / 238 (87.82%)	479 / 482 (99.38%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 238 (4.62%)	66 / 482 (13.69%)	
occurrences (all)	12	87	
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 238 (5.46%)	75 / 482 (15.56%)	
occurrences (all)	13	89	
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 238 (5.04%)	18 / 482 (3.73%)	
occurrences (all)	12	28	
Blood creatinine increased			
subjects affected / exposed	3 / 238 (1.26%)	41 / 482 (8.51%)	
occurrences (all)	3	53	
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 238 (1.68%)	30 / 482 (6.22%)	
occurrences (all)	5	44	
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	20 / 238 (8.40%)	53 / 482 (11.00%)	
occurrences (all)	23	67	
Weight decreased			
subjects affected / exposed	17 / 238 (7.14%)	136 / 482 (28.22%)	
occurrences (all)	17	142	
Vascular disorders			
Hot flush			
subjects affected / exposed	34 / 238 (14.29%)	31 / 482 (6.43%)	
occurrences (all)	38	33	
Hypertension			
subjects affected / exposed	9 / 238 (3.78%)	49 / 482 (10.17%)	
occurrences (all)	9	59	
Lymphoedema			
subjects affected / exposed	3 / 238 (1.26%)	30 / 482 (6.22%)	
occurrences (all)	3	33	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 238 (6.72%)	38 / 482 (7.88%)	
occurrences (all)	17	44	
Dysgeusia			
subjects affected / exposed	14 / 238 (5.88%)	106 / 482 (21.99%)	
occurrences (all)	14	115	
Headache			
subjects affected / exposed	35 / 238 (14.71%)	112 / 482 (23.24%)	
occurrences (all)	44	156	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	4 / 238 (1.68%)	29 / 482 (6.02%)	
occurrences (all)	4	37	
Anaemia			
subjects affected / exposed	11 / 238 (4.62%)	101 / 482 (20.95%)	
occurrences (all)	13	118	
Neutropenia			
subjects affected / exposed	4 / 238 (1.68%)	40 / 482 (8.30%)	
occurrences (all)	4	51	
Thrombocytopenia			

subjects affected / exposed	1 / 238 (0.42%)	63 / 482 (13.07%)	
occurrences (all)	1	84	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 238 (4.62%)	70 / 482 (14.52%)	
occurrences (all)	11	84	
Fatigue			
subjects affected / exposed	65 / 238 (27.31%)	180 / 482 (37.34%)	
occurrences (all)	72	213	
Pyrexia			
subjects affected / exposed	13 / 238 (5.46%)	82 / 482 (17.01%)	
occurrences (all)	14	120	
Oedema peripheral			
subjects affected / exposed	15 / 238 (6.30%)	103 / 482 (21.37%)	
occurrences (all)	16	127	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 238 (4.62%)	25 / 482 (5.19%)	
occurrences (all)	11	29	
Abdominal pain upper			
subjects affected / exposed	7 / 238 (2.94%)	39 / 482 (8.09%)	
occurrences (all)	8	44	
Diarrhoea			
subjects affected / exposed	44 / 238 (18.49%)	172 / 482 (35.68%)	
occurrences (all)	55	238	
Constipation			
subjects affected / exposed	31 / 238 (13.03%)	74 / 482 (15.35%)	
occurrences (all)	42	81	
Dyspepsia			
subjects affected / exposed	12 / 238 (5.04%)	29 / 482 (6.02%)	
occurrences (all)	12	33	
Dry mouth			
subjects affected / exposed	17 / 238 (7.14%)	55 / 482 (11.41%)	
occurrences (all)	19	62	
Nausea			

subjects affected / exposed	69 / 238 (28.99%)	157 / 482 (32.57%)	
occurrences (all)	84	211	
Vomiting			
subjects affected / exposed	30 / 238 (12.61%)	88 / 482 (18.26%)	
occurrences (all)	32	121	
Stomatitis			
subjects affected / exposed	28 / 238 (11.76%)	286 / 482 (59.34%)	
occurrences (all)	37	493	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	25 / 238 (10.50%)	105 / 482 (21.78%)	
occurrences (all)	25	124	
Cough			
subjects affected / exposed	27 / 238 (11.34%)	129 / 482 (26.76%)	
occurrences (all)	28	169	
Oropharyngeal pain			
subjects affected / exposed	7 / 238 (2.94%)	29 / 482 (6.02%)	
occurrences (all)	7	40	
Epistaxis			
subjects affected / exposed	3 / 238 (1.26%)	86 / 482 (17.84%)	
occurrences (all)	3	117	
Pneumonitis			
subjects affected / exposed	0 / 238 (0.00%)	73 / 482 (15.15%)	
occurrences (all)	0	81	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 238 (1.26%)	39 / 482 (8.09%)	
occurrences (all)	3	41	
Alopecia			
subjects affected / exposed	12 / 238 (5.04%)	51 / 482 (10.58%)	
occurrences (all)	13	57	
Nail disorder			
subjects affected / exposed	1 / 238 (0.42%)	40 / 482 (8.30%)	
occurrences (all)	1	41	
Pruritus			

subjects affected / exposed	11 / 238 (4.62%)	64 / 482 (13.28%)	
occurrences (all)	12	76	
Rash			
subjects affected / exposed	16 / 238 (6.72%)	190 / 482 (39.42%)	
occurrences (all)	20	278	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 238 (2.52%)	25 / 482 (5.19%)	
occurrences (all)	6	26	
Depression			
subjects affected / exposed	11 / 238 (4.62%)	28 / 482 (5.81%)	
occurrences (all)	12	32	
Insomnia			
subjects affected / exposed	21 / 238 (8.82%)	68 / 482 (14.11%)	
occurrences (all)	24	70	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	41 / 238 (17.23%)	107 / 482 (22.20%)	
occurrences (all)	45	155	
Back pain			
subjects affected / exposed	25 / 238 (10.50%)	81 / 482 (16.80%)	
occurrences (all)	27	98	
Musculoskeletal chest pain			
subjects affected / exposed	10 / 238 (4.20%)	38 / 482 (7.88%)	
occurrences (all)	14	42	
Bone pain			
subjects affected / exposed	15 / 238 (6.30%)	31 / 482 (6.43%)	
occurrences (all)	20	34	
Musculoskeletal pain			
subjects affected / exposed	17 / 238 (7.14%)	30 / 482 (6.22%)	
occurrences (all)	19	33	
Myalgia			
subjects affected / exposed	16 / 238 (6.72%)	35 / 482 (7.26%)	
occurrences (all)	20	40	
Pain in extremity			

subjects affected / exposed	26 / 238 (10.92%)	52 / 482 (10.79%)	
occurrences (all)	32	70	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	21 / 238 (8.82%)	53 / 482 (11.00%)	
occurrences (all)	26	73	
Urinary tract infection			
subjects affected / exposed	5 / 238 (2.10%)	49 / 482 (10.17%)	
occurrences (all)	5	60	
Upper respiratory tract infection			
subjects affected / exposed	6 / 238 (2.52%)	32 / 482 (6.64%)	
occurrences (all)	6	44	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	31 / 238 (13.03%)	148 / 482 (30.71%)	
occurrences (all)	38	169	
Hypercholesterolaemia			
subjects affected / exposed	2 / 238 (0.84%)	50 / 482 (10.37%)	
occurrences (all)	2	62	
Hypertriglyceridaemia			
subjects affected / exposed	3 / 238 (1.26%)	29 / 482 (6.02%)	
occurrences (all)	3	35	
Hyperglycaemia			
subjects affected / exposed	5 / 238 (2.10%)	69 / 482 (14.32%)	
occurrences (all)	5	91	
Hypokalaemia			
subjects affected / exposed	4 / 238 (1.68%)	39 / 482 (8.09%)	
occurrences (all)	4	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2010	Amendment 1 was issued after 157 patients were randomized. Subsequently, another 567 patients were randomized to the study. The purpose was: to implement program-level and study operational changes. Program-level changes included addition of guidelines on hepatitis B virus and hepatitis C virus management, detailing hyperglycemia management and everolimus administration, and modification of guidance on the usage of CYP3A4 and/or P-glycoprotein inducers and inhibitors, study operational changes included the addition of a pre-randomization process; to clarify elements in the protocol, such as the data source for primary endpoint and definition of a "lines" in exclusion criterion; to modify exclusion criteria of patients with history of brain and central nervous system metastases and Eastern cooperative oncology group performance status time-to deterioration analysis.
12 December 2011	Amendment 2 was issued after the completion of the primary CSR. 103 patients were still receiving study therapy at the time of this amendment. The study had met its primary endpoint PFS at the interim analysis. The purpose was to make interim OS analyses results available by independent data monitoring committee (IDMC) to health authorities on their request to fully evaluate the benefit-risk assessment of everolimus in breast cancer; to add one additional interim analysis after 275 OS events (70% of the targeted total) in order to assess more mature survival; to change the frequency of tumor assessments to every 12 weeks and as clinically indicated, until disease progression after approximately 528 PFS events have been documented per response evaluation criteria in solid tumors (RECIST) by local assessment.
23 April 2014	Amendment 3 was issued after the final OS CSR. Nine patients were still receiving study therapy at the time of this amendment. The study had met its primary (PFS) and reported key secondary endpoints (OS).The purpose of the amendment was to close out the study after collecting required safety data from the patients who were still receiving study treatment and transitioning them to commercially available drugs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: