Clinical trial results:
A Phase IIIB, Multi-Center, Open Label Study For Postmenopausal Women With Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Treated With Everolimus (RAD001) in Combination With Exemestane

Summary

EudraCT number	2011-006111-62
Trial protocol	DE
Global end of trial date	26 November 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	CRAD001JDE49

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01626222
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	26 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the Overall Response Rate (ORR) in postmenopausal women with hormone receptor positive breast cancer progressing following prior therapy with NSAIs treated with the combination of Everolimus and Exemestane.

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	25 June 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	Germany: 299
Worldwide total number of subjects	299
EEA total number of subjects	299

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)	134
From 65 to 84 years	163
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All screening evaluations were to be performed within 28 days prior to treatment Day 1.

Period 1

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

Arms

Arm title	everolimus + exemestane

Arm description:

Patients were treated with daily doses of 10 mg everolimus orally and 25 mg exemestane orally

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

Dosage and administration details:

Everolimus is formulated as tablets of 10mg and 5mg strength for oral administration. Everolimus was started on study Day 1 (baseline) and continued for 48 weeks or until progression of disease, unacceptable toxicity, death, or study discontinuation for any other reason.

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

Dosage and administration details:

Patients were treated with daily doses of 25 mg exemestane orally. Exemestane was started on study Day 1 (baseline) and continued for 48 weeks or until progression of disease, unacceptable toxicity, death, or
study discontinuation for any other reason.

Number of subjects in period 1	everolimus + exemestane
Started	299
Completed	36
Not completed	263
Adverse event, serious fatal	24
Abnormal laboratory value(s)	3
Consent withdrawn by subject	19
Disease progression	116

Adverse event, non-fatal	74
New cancer therapy	5
Administrative problems	6
Missing data on treatment continuation	8
Lost to follow-up	2
Protocol deviation	6

Baseline characteristics

Reporting groups	
Reporting group title	everolimus + exemestane
Reporting group description:	
Patients were treated with daily doses of 10 mg everolimus orally and 25 mg exemestane orally	

Reporting group values	everolimus + exemestane	Total	
Number of subjects	299	299	
Age categorical Units: Subjects			
< 65 years	134	134	
≥ 65 years	165	165	
Age continuous Units: years			
arithmetic mean	65.4		
standard deviation	± 9.3	-	
Gender categorical Units: Subjects			
Female	299	299	
Male	0	0	

End points

End points reporting groups

Reporting group title	everolimus + exemestane
Reporting group description:	
Patients were treated with daily doses of 10 mg everolimus orally and 25 mg exemestane orally	
Subject analysis set title	Full Analysis Set 1 (FAS1)
Subject analysis set type	Full analysis
Subject analysis set description:	
consists of all patients to whom treatment was assigned and who received at least 1 dose of study drug with the exception of patients from 2 sites due to an issue of GCP non-compliance	
Subject analysis set title	Full Analysis Set 2 (FAS2)
Subject analysis set type	Full analysis
Subject analysis set description:	
consists of all patients to whom treatment was assigned and who received at least 1 dose of study drug.	
Subject analysis set title	Per-Protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
consists of a subset of patients of the FAS1 who did not show major protocol deviations	

Primary: Overall Response Rate (ORR) after 24 weeks of treatment

End point title	Overall Response Rate (ORR) after 24 weeks of treatment[1]
End point description:	
The Overall response rate (ORR) is the proportion of patients with a best overall response of confirmed complete (CR) or partial (PR) response by Week 24. The best overall response is determined from the sequence of investigator overall lesion responses according to RECIST 1.1. To be assigned a best overall response of CR at least two determinations of CR at least 4 weeks apart before progression are required. To be assigned a best overall response of PR at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) are required.	
End point type	Primary
End point timeframe:	
24 weeks	

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 additional statistical analyses have been specified for this primary end point.

End point values	Full Analysis Set 1 (FAS1)	Full Analysis Set 2 (FAS2)	Per-Protocol Set (PPS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	281[2]	299[3]	162[4]	
Units: Percentage				
number (confidence interval 95%)	8.9 (5.8 to 12.9)	8.4 (5.5 to 12.1)	9.3 (5.3 to 14.8)	

Notes:

[2] - Percentage of patients with best overall response CR or PR

[3] - Percentage of patients with best overall response CR or PR

[4] - Percentage of patients with best overall response CR or PR

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) after 48 weeks of treatment

End point title	Progression free survival (PFS) after 48 weeks of treatment

End point description:

Progression-free survival (PFS) is the time from date of start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Full Analysis Set 1 (FAS1)			
Subject group type	Subject analysis set			
Number of subjects analysed	281[5]			
Units: percentage				
number (not applicable)	19.3			

Notes:

[5] - Kaplan-Meier estimates of %]of patients surviving without progression (PFS)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) after 48 weeks of treatment

End point title	Overall Response Rate (ORR) after 48 weeks of treatment

End point description:

The ORR by Week 48 will be derived from the sequence of overall lesion responses as described for the primary efficacy variable. The ORR by Week 48 will be summarized using frequency tables presenting absolute and relative frequencies together with appropriate confidence intervals

End point type	Secondary

End point timeframe:

48 weeks

End point values	Full Analysis Set 1 (FAS1)			
Subject group type	Subject analysis set			
Number of subjects analysed	281[6]			
Units: percentage				
number (confidence interval 95%)	10.3 (7 to 14.5)			

Notes:

[6] - Percentage of patients with best overall response CR or PR

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) after 48 weeks of treatment

End point title	Overall survival (OS) after 48 weeks of treatment

End point description:

Overall survival (OS) is defined as the time from date of start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact. OS will be summarized using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Full Analysis Set 1 (FAS1)			
Subject group type	Subject analysis set			
Number of subjects analysed	281[7]			
Units: percentage				
number (not applicable)	66.9			

Notes:

[7] - Kaplan-Meier estimates of % of patients surviving (OS)

Statistical analyses

No statistical analyses for this end point

Secondary: Resource utilization

End point title	Resource utilization

End point description:

Data relating to Resource Utilization will be used for the purpose of economic evaluation, which will be carried out and reported as a separate activity. The study population receiving RAD001 plus Exemestane will be compared to alternative cohorts (e.g., purely endocrine treatment with Fulvestrant monotherapy, Exemestane monotherapy or chemotherapy, e.g. Capecitabine) using a Markov model. For each alternative therapy option, median PFS, OS and health-related quality of life will be determined by a systematic review of literature or databases.

End point type	Secondary

End point timeframe:

48 weeks

End point values	everolimus + exemestane			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: participants				
number (not applicable)				

Notes:

[8] - Analysis of health resource cancelled due to difficulties obtaining an adequate reference dataset.

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of life (HRQoL) assessed using the EORTC QLQ-C30

End point title	Health-related quality of life (HRQoL) assessed using the EORTC QLQ-C30

End point description:

Health-related quality of life (HRQoL) will be assessed using the EORTC QLQ-C30 .
EORTC QLQ-C30 scales range from 0 to 100. High scores for global health status/QoL scale and for 5 functional scales (physical to social functioning) represent high QoL/level of functioning. High scores for other scales (fatigue to financial difficulties) represent high levels of symptomatology/problems.

End point type	Secondary

End point timeframe:

48 weeks/ end of treatment (EOT)

End point values	Full Analysis Set 1 (FAS1)			
Subject group type	Subject analysis set			
Number of subjects analysed	281[9]			
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Physical functioning Baseline	66.6 (± 24.6)			
Physical functioning EOT	64.1 (± 25.4)			
Role functioning Baseline	55.9 (± 35.4)			
Role functioning EOT	52.4 (± 31.2)			
Emotional functioning Baseline	62.7 (± 24.3)			
Emotional functioning EOT	58.5 (± 24.3)			
Cognitive functioning Baseline	79.6 (± 24.4)			
Cognitive functioning EOT	72.3 (± 24.4)			
Social functioning Baseline	66.9 (± 30.2)			
Social functioning EOT	58.6 (± 30.2)			
Fatigue Baseline	47.4 (± 29.1)			
Fatigue EOT	54.7 (± 27.9)			
Nausea and vomiting Baseline	11 (± 19.8)			
Nausea and vomiting EOT	14.8 (± 24.9)			
Pain Baseline	43.6 (± 31.7)			
Pain EOT	43.1 (± 31.4)			
Dyspnoea Baseline	34.8 (± 33.2)			
Dyspnoea EOT	44.3 (± 33.4)			
Insomnia Baseline	43.8 (± 34.4)			
Insomnia EOT	50.5 (± 32.3)			

Appetite loss Baseline	28.2 (± 33.6)			
Appetite loss EOT	40.4 (± 36.8)			
Constipation Baseline	14.6 (± 26.5)			
Constipation EOT	14.8 (± 28.9)			
Diarrhea Baseline	12.6 (± 23.3)			
Diarrhea EOT	20 (± 30)			
Financial difficulties Baseline	16.5 (± 27.3)			
Financial difficulties EOT	24.5 (± 32.6)			

Notes:

[9] - Baseline N = 280; EOT N = 176

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 are reported in this record from 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

Reporting groups

Reporting group title	All patients

Reporting group description:

All patients

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	142 / 299 (47.49%)		
number of deaths (all causes)	36		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Enchondroma			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant ascites			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malignant neoplasm progression			

subjects affected / exposed	18 / 299 (6.02%)		
occurrences causally related to treatment / all	0 / 18		
deaths causally related to treatment / all	0 / 13		
Malignant pleural effusion			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to bone			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metastases to central nervous system			
subjects affected / exposed	4 / 299 (1.34%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Metastases to lung			
subjects affected / exposed	3 / 299 (1.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Metastases to peritoneum			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to spine			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastasis			

subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Circulatory collapse				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	3 / 299 (1.00%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphoedema				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Shock haemorrhagic				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Venous thrombosis limb				

subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Eyelid operation			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Fatigue			
subjects affected / exposed	7 / 299 (2.34%)		
occurrences causally related to treatment / all	5 / 8		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	21 / 299 (7.02%)		
occurrences causally related to treatment / all	8 / 27		
deaths causally related to treatment / all	2 / 5		
Generalised oedema			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Influenza like illness			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Multi-organ failure			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Oedema peripheral			
subjects affected / exposed	3 / 299 (1.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	6 / 299 (2.01%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Asphyxia			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	12 / 299 (4.01%)		
occurrences causally related to treatment / all	3 / 14		
deaths causally related to treatment / all	0 / 2		
Dyspnoea exertional			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Haemoptysis			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Interstitial lung disease			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Orthopnoea			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	13 / 299 (4.35%)			
occurrences causally related to treatment / all	2 / 14			
deaths causally related to treatment / all	0 / 1			
Pneumonia aspiration				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	10 / 299 (3.34%)			
occurrences causally related to treatment / all	11 / 11			
deaths causally related to treatment / all	1 / 1			
Pneumothorax				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary congestion				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Delusional disorder, unspecified type				

subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depressed mood				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depressive delusion				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Emotional distress				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood bilirubin increased				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood glucose fluctuation				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Body temperature increased				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				

subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nutritional condition abnormal				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Red blood cell count decreased				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Waist circumference increased				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				

Clavicle fracture				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				

subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Cardiovascular insufficiency				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Alcohol induced persisting dementia				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cranial nerve disorder				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Disturbance in attention				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				

subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Grand mal convulsion				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	3 / 299 (1.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial pressure increased				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neurological decompensation				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Paraesthesia				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraparesis				

subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraplegia				
subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudoradicular syndrome				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vocal cord paralysis				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	6 / 299 (2.01%)			
occurrences causally related to treatment / all	4 / 7			
deaths causally related to treatment / all	0 / 0			
Bone marrow failure				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy mediastinal			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenomegaly			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulcerative keratitis			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 299 (1.34%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		

Aphagia			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Colitis			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	6 / 299 (2.01%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Intestinal obstruction			

subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	10 / 299 (3.34%)			
occurrences causally related to treatment / all	8 / 12			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				
subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	4 / 299 (1.34%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Swollen tongue				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	13 / 299 (4.35%)			
occurrences causally related to treatment / all	8 / 14			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis				

subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	4 / 299 (1.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 4			
Hepatomegaly				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatorenal syndrome				
subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Jaundice				
subjects affected / exposed	3 / 299 (1.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin reaction				

subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 299 (1.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Renal failure acute			
subjects affected / exposed	3 / 299 (1.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 299 (1.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Patellofemoral pain syndrome			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Bronchitis			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	2 / 299 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cystitis escherichia			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye abscess			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile infection			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 299 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis norovirus			

subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	5 / 299 (1.67%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Lymphangitis				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	17 / 299 (5.69%)			
occurrences causally related to treatment / all	9 / 18			
deaths causally related to treatment / all	1 / 2			
Pneumonia streptococcal				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 299 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Tooth abscess				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	4 / 299 (1.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Cachexia				
subjects affected / exposed	3 / 299 (1.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Decreased appetite				
subjects affected / exposed	4 / 299 (1.34%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	5 / 299 (1.67%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 1			
Electrolyte imbalance				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypovolaemia				
subjects affected / exposed	1 / 299 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	281 / 299 (93.98%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 299 (8.70%)		
occurrences (all)	30		
Aspartate aminotransferase increased			
subjects affected / exposed	27 / 299 (9.03%)		
occurrences (all)	30		
Gamma-glutamyltransferase increased			
subjects affected / exposed	18 / 299 (6.02%)		
occurrences (all)	18		
Weight decreased			
subjects affected / exposed	44 / 299 (14.72%)		
occurrences (all)	45		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	55 / 299 (18.39%)		
occurrences (all)	55		
Headache			
subjects affected / exposed	34 / 299 (11.37%)		
occurrences (all)	38		
Polyneuropathy			
subjects affected / exposed	15 / 299 (5.02%)		
occurrences (all)	15		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	51 / 299 (17.06%)		
occurrences (all)	61		
Leukopenia			
subjects affected / exposed	22 / 299 (7.36%)		
occurrences (all)	25		
Thrombocytopenia			

subjects affected / exposed	21 / 299 (7.02%)		
occurrences (all)	23		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	103 / 299 (34.45%)		
occurrences (all)	108		
General physical health deterioration			
subjects affected / exposed	18 / 299 (6.02%)		
occurrences (all)	18		
Oedema peripheral			
subjects affected / exposed	48 / 299 (16.05%)		
occurrences (all)	54		
Pyrexia			
subjects affected / exposed	25 / 299 (8.36%)		
occurrences (all)	26		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	20 / 299 (6.69%)		
occurrences (all)	22		
Aphthous stomatitis			
subjects affected / exposed	27 / 299 (9.03%)		
occurrences (all)	35		
Constipation			
subjects affected / exposed	25 / 299 (8.36%)		
occurrences (all)	27		
Diarrhoea			
subjects affected / exposed	75 / 299 (25.08%)		
occurrences (all)	97		
Dry mouth			
subjects affected / exposed	19 / 299 (6.35%)		
occurrences (all)	19		
Nausea			
subjects affected / exposed	72 / 299 (24.08%)		
occurrences (all)	78		
Stomatitis			

subjects affected / exposed	146 / 299 (48.83%)		
occurrences (all)	177		
Vomiting			
subjects affected / exposed	34 / 299 (11.37%)		
occurrences (all)	39		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	51 / 299 (17.06%)		
occurrences (all)	55		
Dyspnoea			
subjects affected / exposed	65 / 299 (21.74%)		
occurrences (all)	68		
Epistaxis			
subjects affected / exposed	43 / 299 (14.38%)		
occurrences (all)	52		
Pneumonitis			
subjects affected / exposed	15 / 299 (5.02%)		
occurrences (all)	15		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	26 / 299 (8.70%)		
occurrences (all)	26		
Dry skin			
subjects affected / exposed	23 / 299 (7.69%)		
occurrences (all)	25		
Nail disorder			
subjects affected / exposed	16 / 299 (5.35%)		
occurrences (all)	16		
Pruritus			
subjects affected / exposed	29 / 299 (9.70%)		
occurrences (all)	30		
Rash			
subjects affected / exposed	67 / 299 (22.41%)		
occurrences (all)	75		
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	26 / 299 (8.70%) 28		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all)	 32 / 299 (10.70%) 35 20 / 299 (6.69%) 21 27 / 299 (9.03%) 27		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 24 / 299 (8.03%) 24		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all)	 74 / 299 (24.75%) 78 15 / 299 (5.02%) 15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2012	The following changes were introduced: • Bone scans could be replaced by whole body CT, provided that this was local standard. • Laboratory evaluations were to be performed according to local standard. • CT for chest, abdomen, pelvis could be replaced by MRI, if CT was clinically contraindicated, e.g., allergy/sensitivity to the radiographic contrast media, metastatic presentation. • Local radiotherapy was allowed during the study duration for analgesic purpose or for lytic lesions at risk of fracture. • The European Medicines Agency (EMA) assessment report for Afinitor states that the indication should be restricted to patients without symptomatic visceral disease in order to avoid the possibility of undertreatment of patients who should receive chemotherapy. As there is no common consensus of the definition of symptomatic visceral disease it was added in the protocol that the prescription of everolimus and exemestane was to follow exclusively the assessment of the patient's individual medical need. • Details concerning the trial drug accounting process as well as a patient diary were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported