Clinical trial results:
A Phase IV multicenter, open label study of postmenopausal women with estrogen receptor-positive locally advanced or metastatic breast cancer treated with everolimus (RAD001) in combination with exemestane, with exploratory epigenetic marker analysis (4EVERUK)

Summary

EudraCT number	2012-003689-41
Trial protocol	GB
Global end of trial date	15 August 2016

Results information

Result version number	v1 (current)
This version publication date	30 August 2017
First version publication date	30 August 2017

Trial information

Trial identification

Sponsor protocol code	CRAD001YGB11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01743560
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 6132411111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 6132411111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2016
Global end of trial reached?	Yes
Global end of trial date	15 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the Overall Response Rate (ORR) at 48 weeks to everolimus (10 mg daily p.o.) and exemestane (25 mg daily p.o.) treatment in postmenopausal women with ER+ BC who have previously experienced recurrence or progression on NSAI therapy.

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	31 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	33
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Sixty-seven patients were screened and 52 patients were enrolled. Forty-nine patients had ≥ 1 dose study drug and were considered as Started

Period 1

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

Arms

Arm title	Everolimus and Exemestane

Arm description:

Postmenopausal women diagnosed with oestrogen receptor positive locally advanced or metastatic breast cancer will receive everolimus at a dose of 10mg daily p.o. and exemestane 25mg daily p.o.

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:

5 mg tablets supplied and dosage was 10 mg (2 × 5 mg) p.o. per day

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 tablets purchased locally and dosage was 1 tablet 25 mg p.o. per day

Number of subjects in period 1	Everolimus and Exemestane
Started	49
Completed	9
Not completed	40
Consent withdrawn by subject	2
Disease progression	26
Adverse event, non-fatal	8
Death	3
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus and Exemestane
Reporting group description:	
Postmenopausal women diagnosed with oestrogen receptor positive locally advanced or metastatic breast cancer will receive everolimus at a dose of 10mg daily p.o. and exemestane 25mg daily p.o.	

Reporting group values	Everolimus and Exemestane	Total	
Number of subjects	49	49	
Age categorical Units: Subjects			
Adults (18-64 years)	33	33	
From 65-84 years	16	16	
Age Continuous Units: years			
arithmetic mean	61.3		
standard deviation	± 8.71	-	
Gender, Male/Female Units: Subjects			
Female	49	49	
Male	0	0	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	48	48	
Other	1	1	
Study Specific Characteristic | Weight Units: kg			
arithmetic mean	71.1		
standard deviation	± 15.44	-	

End points

End points reporting groups

Reporting group title	Everolimus and Exemestane
Reporting group description: Postmenopausal women diagnosed with oestrogen receptor positive locally advanced or metastatic breast cancer will receive everolimus at a dose of 10mg daily p.o. and exemestane 25mg daily p.o.	
Subject analysis set title	Week 12
Subject analysis set type	Sub-group analysis
Subject analysis set description: Change from baseline at week 12	
Subject analysis set title	Week 24
Subject analysis set type	Sub-group analysis
Subject analysis set description: Change from baseline at Week 24	
Subject analysis set title	Week 36
Subject analysis set type	Sub-group analysis
Subject analysis set description: Change from baseline at week 36	
Subject analysis set title	Week 48
Subject analysis set type	Sub-group analysis
Subject analysis set description: Change from baseline at week 48	
Subject analysis set title	Day 1
Subject analysis set type	Sub-group analysis
Subject analysis set description: Baseline	
Subject analysis set title	Week 12
Subject analysis set type	Sub-group analysis
Subject analysis set description: Week 12 on treatment	
Subject analysis set title	Week 24
Subject analysis set type	Sub-group analysis
Subject analysis set description: Week 24 on treatment	
Subject analysis set title	Week 36
Subject analysis set type	Sub-group analysis
Subject analysis set description: Week 36 on treatament	
Subject analysis set title	Week 48
Subject analysis set type	Sub-group analysis
Subject analysis set description: Week 48 on treatment	
Subject analysis set title	Week 12
Subject analysis set type	Sub-group analysis
Subject analysis set description: Change from baseline at week 12	
Subject analysis set title	Week 24
Subject analysis set type	Sub-group analysis
Subject analysis set description: Change from baseline at Week 24	

Subject analysis set title	Week 36
Subject analysis set type	Sub-group analysis
Subject analysis set description: Change from baseline at week 36	
Subject analysis set title	Week 48
Subject analysis set type	Sub-group analysis
Subject analysis set description: Change from baseline at week 48	

Primary: Best overall response of everolimus and exemestane treatment in postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer

End point title	Best overall response of everolimus and exemestane treatment in postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer[1]

End point description:

The best Overall Response (OR) for each patient is determined from the sequence of investigator overall lesion responses according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1.). To be assigned a best OR of Complete Responese (CR) at least two determinations of CR at least 4 weeks apart before progression are required. To be assigned a best OR of Partial Response (PR) at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) are required.The Overall Response Rate (ORR) was defined as the proportion of patients with a best OR of confirmed CR or PR by week 48.

End point type	Primary

End point timeframe:

At 48 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 statistical hypothesis testing was done for primary endpoint

End point values	Everolimus and Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: participants				
Patients with measurable disease at baseline	39			
Patients with non-measurable disease at baseline	10			
Best at WK 48 - Complete Response (CR)	0			
Best at WK 48 - Partial Response (PR)	7			
Best at WK 48 - Stable Disease (SD)	18			
Best at WK 48 - Progressive Disease (PD)	15			
Unknown	1			
Missing	8			

Statistical analyses

No statistical analyses for this end point

Primary: Overall response rate of everolimus and exemestane treatment in

postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer

End point title	Overall response rate of everolimus and exemestane treatment in postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer[2]

End point description:

The Overall Response Rate (ORR) was defined as the proportion of patients with a best OR of confirmed CR or PR by week 48. Treatment success is defined as: The best Overall Response (OR) for each patient is determined from the sequence of investigator overall lesion responses according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1.). To be assigned a best OR of Complete Responese (CR) at least two determinations of CR at least 4 weeks apart before progression are required. To be assigned a best OR of Partial Response (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:

At 48 weeks

Notes:

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

End point values	Everolimus and Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage of participants				
number (confidence interval 95%)	14.3 (6 to 27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Events as per Investigators - FAS

End point title	Progression-free Survival (PFS) Events as per Investigators - FAS

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. Tumor assessment and response was evaluated according to RECIST v1.1Response was assessed by local radiology review.

End point type	Secondary

End point timeframe:

Start of treatment to the date of event defined as first documented progression due to any cause up to approximately 48 weeks

End point values	Everolimus and Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Number of events				
Deaths	8			
Progression of disease	25			
Number of censored observations	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) by Median Time in weeks as per Investigators - FAS

End point title	Progression-free Survival (PFS) by Median Time in weeks as per Investigators - FAS

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. Tumor assessment and response was evaluated according to RECIST v1.1Response was assessed by local radiology review.

End point type	Secondary

End point timeframe:

Start of treatment to the date of event defined as first documented progression due to any cause up to approximately 48 weeks

End point values	Everolimus and Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: weeks				
median (confidence interval 95%)	23.6 (12.71 to 34.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) - % Event-free probability estimate - FAS

End point title	Progression-free Survival (PFS) - % Event-free probability estimate - FAS

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. Tumor assessment and response was evaluated according to RECIST v1.1Response was assessed by local radiology review.

The PFS was analyzed using the Kaplan Meier method.

End point type	Secondary

End point timeframe:

Start of treatment to the date of event defined as first documented progression due to any cause up to approximately 48 weeks

End point values	Everolimus and Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage of participants				
number (confidence interval 95%)				
Event free at 12 weeks	67.9 (51.82 to 79.56)			
Event free at 24 weeks	49.1 (32.98 to 63.44)			
Event free at 36 weeks	28.9 (15.42 to 43.87)			
Event free at 48 weeks	18.4 (7.38 to 33.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Events as per Investigators - FAS

End point title	Overall Survival (OS) Events as per Investigators - FAS

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. Time to median OS was not estimable.

End point type	Secondary

End point timeframe:

Start of treatment to the date of death up to approximately 48 weeks

End point values	Everolimus and Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Number of events				
Deaths	8			
Number of censored observations	41			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - % Event-free probability estimate - FAS

End point title	Overall Survival (OS) - % Event-free probability estimate - FAS

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.

End point type	Secondary

End point timeframe:

Start of treatment to the date of death up to approximately 48 weeks

End point values	Everolimus and Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage of participants				
number (confidence interval 95%)				
Event free at 12 weeks	93.3 (80.57 to 97.78)			
Event free at 24 weeks	83.9 (66.92 to 92.6)			
Event free at 36 weeks	74.2 (53.02 to 86.88)			
Event free at 48 weeks	74.2 (53.02 to 86.88)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life (EORTC Quality of Life Questionnaire of cancer patients QLQ-C30)

End point title	Quality of life (EORTC Quality of Life Questionnaire of cancer patients QLQ-C30)

End point description:

The QLQ-C30 is composed of multi-item scales and single-item measures including 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. High scale score=higher response level; a high score for a functional scale=a healthy level of function, high score for the global health status/QoL=high quality of life but a high score for a symptom scale / item=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. Results should be interpreted with caution as the numbers of patients with available data over time were limited, and because of high variances as evidenced by large standard deviations

End point type	Secondary

End point timeframe:

Baseline 12,24,36,48 weeks

End point values	Week 12	Week 24	Week 36	Week 48
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	17	13	28
Units: scores				
arithmetic mean (standard deviation)				
Global health status/QoL (27,16,13,26)	-9 (± 22.04)	-3.6 (± 19.71)	1.9 (± 16.37)	-8.3 (± 22.48)
Physical functioning(27,17,13,28)	-5.1 (± 19.16)	-1 (± 14.52)	4.9 (± 13.79)	-10.8 (± 29.97)
Role functioning (26,16,12,27)	-4.5 (± 33.19)	3.1 (± 23.74)	8.3 (± 23.03)	-12.3 (± 30.52)
Emotional functioning(27,16,13,26)	2.6 (± 21.36)	-3.1 (± 14.87)	7.5 (± 9.9)	0.6 (± 21.59)
Cognitive functioning (27,16,13,27)	-8.6 (± 21.37)	-5.2 (± 17.97)	1.3 (± 22.01)	-3.7 (± 21.35)
Social functioning(27,16,13,26)	-9.9 (± 25)	-9.4 (± 24.32)	3.8 (± 15.45)	-14.7 (± 31.74)
Fatigue (27,17,13,28)	8.6 (± 26.92)	9.5 (± 15.93)	0.9 (± 16.64)	7.3 (± 24.66)
Nausea/ vomiting (27,17,13,28)	-1.2 (± 15.96)	2.9 (± 16.91)	-3.8 (± 15.45)	-2.4 (± 23.88)
Pain(27,17,13,28)	1.2 (± 26.12)	3.9 (± 24.67)	-1.3 (± 20.93)	0.6 (± 24.64)
Dyspnea(27,16,13,28)	18.5 (± 37.36)	8.3 (± 25.82)	2.6 (± 25.32)	10.7 (± 27.3)
Insomnia(27,17,13,28)	3.7 (± 26.69)	2 (± 29.98)	0 (± 23.57)	-3.6 (± 37.78)
Appetite loss(27,17,13,28)	30.9 (± 40.22)	23.5 (± 28.3)	12.8 (± 28.99)	16.7 (± 35.72)
Constipation(27,17,13,28)	4.9 (± 32.95)	11.8 (± 28.73)	10.3 (± 21.01)	8.3 (± 19.51)
Diarrhea(27,16,13,27)	4.9 (± 25.66)	8.3 (± 37.52)	-5.1 (± 22.96)	7.4 (± 28.24)
Financial problems (27,16,13,26)	-1.2 (± 21.64)	-10.4 (± 26.44)	-10.3 (± 21.01)	-2.6 (± 18.67)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patient responses in EuroQoL 5-dimension questionnaire - FAS

End point title	Percentage of patient responses in EuroQoL 5-dimension questionnaire - FAS

End point description:

The EQ-5D is a standardized instrument to assess health state values that has been developed, validated and published by the EuroQol Group (EuroQol Group 1990). The EQ-5D essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Percentage of participants' responses were presented by visits. Results should be interpreted with caution as the numbers of patients with available data over time were limited, and because of high variances as evidenced by large standard deviations.

End point type	Secondary

End point timeframe:

Baseline 12,24,36,48 weeks

End point values	Day 1	Week 12	Week 24	Week 36
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	49	49	49
Units: Percentage of participants				
number (not applicable)				
Mobility-no problem	38.8	20.4	18.4	14.3
Mobility-slight problem	18.4	14.3	10.2	8.2
Mobility-moderate problem	32.7	20.4	8.2	2
Mobility-severe problem	6.1	2	0	2
Mobility-unable to walk	0	0	0	0
Self-care - no problem	69.4	44.9	34.7	24.5
Self-care - slight problem	18.4	4.1	0	0
Self-care - moderate problem	6.1	8.2	2	2
Self-care -severe problem	2	0	0	0
Self-care - unable	0	0	0	0
Usual activities - no problems	30.6	14.3	22.4	14.3
Usual activities - slight problems	22.4	16.3	2	8.2
Usual activities - moderate problems	28.6	22.4	12.2	2
Usual activities - severe problems	10.2	4.1	0	2
Usual activities -unable to do	4.1	0	0	0
Pain/discomfort - none	20.4	14.3	10.2	12.2
Pain/discomfort - slight	30.6	16.3	18.4	8.2
Pain/discomfort - moderate	40.8	22.4	8.2	6.1
Pain/discomfort - severe	4.1	4.1	0	0
Pain/discomfort - extreme	0	0	0	0
Anxiety/depression - none	44.9	22.4	18.4	16.3
Anxiety/depression - slight	34.7	22.4	12.2	10.2
Anxiety/depression - moderate	16.3	12.2	6.1	0
Anxiety/depression - severe	0	0	0	0
Anxiety/depression - extreme	0	0	0	0

End point values	Week 48			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: Percentage of participants				
number (not applicable)				
Mobility-no problem	16.3			
Mobility-slight problem	16.3			
Mobility-moderate problem	14.3			
Mobility-severe problem	6.1			
Mobility-unable to walk	4.1			
Self-care - no problem	40.8			
Self-care - slight problem	10.2			
Self-care - moderate problem	4.1			
Self-care -severe problem	2			
Self-care - unable	0			
Usual activities - no problems	18.4			
Usual activities - slight problems	14.3			

Usual activities - moderate problems	12.2			
Usual activities - severe problems	6.1			
Usual activities -unable to do	6.1			
Pain/discomfort - none	18.4			
Pain/discomfort - slight	20.4			
Pain/discomfort - moderate	14.3			
Pain/discomfort - severe	4.1			
Pain/discomfort - extreme	0			
Anxiety/depression - none	22.4			
Anxiety/depression - slight	20.4			
Anxiety/depression - moderate	8.2			
Anxiety/depression - severe	6.1			
Anxiety/depression - extreme	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EuroQoL 5-dimension visual analogue scores - FAS

End point title	Change from baseline in EuroQoL 5-dimension visual analogue scores - FAS

End point description:

The EQ-5D is another standardized instrument to assess health state values that has been developed, validated and published by the EuroQol Group (EuroQol Group 1990). The EQ-5D essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The change in EuroQoL EQ-5D overall health state (VAS), from baseline to each post-baseline time point was described with the mean, and 95% CI of the mean. Results should be interpreted with caution as the numbers of patients with available data over time were limited, and because of high variances as evidenced by large standard deviations.

End point type	Secondary

End point timeframe:

Baseline 12,24,36,48 weeks

End point values	Week 12	Week 24	Week 36	Week 48
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	16	12	27
Units: scores				
arithmetic mean (standard deviation)	-7.9 (± 18.98)	-6.1 (± 12.47)	-6.3 (± 10.03)	-11.6 (± 22.58)

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	19.0

Reporting groups

Reporting group title	Everolimus + Exemestane

Reporting group description:

Everolimus + Exemestane

Serious adverse events	Everolimus + Exemestane		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 49 (44.90%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Tachycardia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathy peripheral			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oral pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Vomiting			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Everolimus + Exemestane		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 49 (100.00%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Alanine aminotransferase increased			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		

Blood cholesterol increased			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	4		
Weight decreased			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	6		
Blood creatinine increased			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	6		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	4		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	7		
Headache			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Anaemia			
subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	11		
General disorders and administration site conditions			
Axillary pain			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Fatigue			

subjects affected / exposed	22 / 49 (44.90%)		
occurrences (all)	23		
Mucosal inflammation			
subjects affected / exposed	17 / 49 (34.69%)		
occurrences (all)	18		
Oedema peripheral			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Peripheral swelling			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	22 / 49 (44.90%)		
occurrences (all)	27		
Mouth ulceration			
subjects affected / exposed	11 / 49 (22.45%)		
occurrences (all)	16		
Dyspepsia			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	5		
Dry mouth			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	14 / 49 (28.57%)		
occurrences (all)	15		

Oral pain subjects affected / exposed occurrences (all)	6 / 49 (12.24%) 7		
Stomatitis subjects affected / exposed occurrences (all)	7 / 49 (14.29%) 8		
Vomiting subjects affected / exposed occurrences (all)	8 / 49 (16.33%) 11		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	18 / 49 (36.73%) 19		
Dyspnoea subjects affected / exposed occurrences (all)	11 / 49 (22.45%) 14		
Epistaxis subjects affected / exposed occurrences (all)	8 / 49 (16.33%) 8		
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3		
Productive cough subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3		
Pneumonitis subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	18 / 49 (36.73%) 20		
Pruritus subjects affected / exposed occurrences (all)	6 / 49 (12.24%) 6		
Psychiatric disorders			

Depressed mood			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	5		
Insomnia			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	7		
Arthralgia			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	5		
Joint swelling			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	7		
Musculoskeletal pain			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	5		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	6		
Oral candidiasis			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 49 (32.65%)		
occurrences (all)	18		

Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3		
Hypercalcaemia subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2013	Post-trial treatment was to be captured for all patients when they completed the trial, whether they withdrew early or completed the full treatment duration. All new anticancer therapies given after the last dose of the study drug were to be recorded on CRF pages designed to capture antineoplastic therapies. An interim analysis was included on all patients who commenced treatment in the study by 04-Sep-2013. This first interim analysis included all screening and baseline data. A second interim analysis was planned to be performed after all patients completed 24 weeks of treatment (or prematurely discontinued on or before this time). End of study was extended from Week 48 until patients progressed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported