



Clinical trial results:

A three-arm, randomized, open label, phase II study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in the treatment of postmenopausal women with estrogen receptor positive, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole

Summary

EudraCT number	2012-003757-28
Trial protocol	BE SE GB IE DK ES HU
Global end of trial date	30 July 2018

Results information

Result version number	v3 (current)
This version publication date	20 March 2021
First version publication date	02 June 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CRAD001Y2201
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01783444
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, 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	30 July 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate the hazard ratio (HR) of progression free survival (PFS) for everolimus plus exemestane versus everolimus alone in postmenopausal women with ER-positive, HER2-negative, advanced breast cancer after recurrence or progression on letrozole or anastrozole.

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	26 February 2016
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	Argentina: 16
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Brazil: 24
Country: Number of subjects enrolled	Denmark: 27
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	India: 10
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Lebanon: 18
Country: Number of subjects enrolled	Malaysia: 11
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Turkey: 16
Country: Number of subjects enrolled	United States: 62

Worldwide total number of subjects	309
EEA total number of subjects	91

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)	198
From 65 to 84 years	109
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 84 centers in 18 countries worldwide: Belgium (1), Denmark (6), Hungary (3), Ireland (3), Spain (4), Sweden (6), United Kingdom (3), United States (19), Argentina (6), Brazil (5), Peru (4), India (4), Lebanon (5), Malaysia (2), Russia (3), Thailand (3), Turkey (3) Australia (4)

Pre-assignment

Screening details:

A total of 300 subjects were planned and total of 309 subjects were randomized to everolimus plus exemestane (control arm) (N = 104), everolimus alone (N = 103), or capecitabine (N = 102).

Period 1

Period 1 title	Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus 10 mg + Exemestane 25 mg

Arm description:

Everolimus (10 mg daily) with Exemestane (25 mg daily) (control arm).

Arm type	Active comparator
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, 5 mg tablets for oral use, 10 mg (2 x 5 mg) per day (centrally supplied)

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

Dosage and administration details:

Exemestane, tablets for oral use, 25 mg per day in (locally supplied)

Arm title	Everolimus 10 mg
------------------	------------------

Arm description:

Everolimus (10 mg daily) (investigational arm).

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, 5 mg tablets for oral use, 10 mg (2 x 5 mg) per day (centrally supplied)

Arm title	Capecitabine 1250 mg/m2
------------------	-------------------------

Arm description:

Capecitabine (1250 mg/m² twice daily) for two weeks, followed by one week rest period in 3-weeks cycles (investigational arm).

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

Dosage and administration details:

Capecitabine, tablets for oral use, 1250 mg/m² twice daily for 2 weeks followed by one week rest (3-week-cycle) (locally supplied)

Number of subjects in period 1	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m ²
Started	104	103	102
Safety Set	104	103	102
Completed	0	0	0
Not completed	104	103	102
Adverse event, serious fatal	2	2	2
Consent withdrawn by subject	6	8	9
Physician decision	8	6	5
Adverse event, non-fatal	9	20	19
Administrative problems	2	-	1
Disease Progression	76	66	64
Protocol deviation	1	1	2

Period 2

Period 2 title	Post-Treatment Efficacy Follow-Up Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Everolimus 10 mg + Exemestane 25 mg

Arm description:

Everolimus (10 mg daily) with Exemestane (25 mg daily) (control arm).

Arm type	Active comparator
----------	-------------------

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, 5 mg tablets for oral use, 10 mg (2 x 5 mg) per day (centrally supplied)	
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Exemestane, tablets for oral use, 25 mg per day in (locally supplied)	
Arm title	Everolimus 10 mg
Arm description:	
Everolimus (10 mg daily) (investigational arm).	
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, 5 mg tablets for oral use, 10 mg (2 x 5 mg) per day (centrally supplied)	
Arm title	Capecitabine 1250 mg/m2
Arm description:	
Capecitabine (1250 mg/m2 twice daily) for two weeks, followed by one week rest period in 3-weeks cycles (investigational arm).	
Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Capecitabine, tablets for oral use, 1250 mg/m ² twice daily for 2 weeks followed by one week rest (3-week-cycle) (locally supplied)	

Number of subjects in period 2	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m2
Started	96	93	91
Completed	0	0	0
Not completed	96	93	91
Adverse event, serious fatal	9	7	5
Consent withdrawn by subject	4	8	8
Followup phase completed as per protocol	69	53	52

New cancer therapy	7	16	15
Administrative problems	-	1	-
Disease Progression	7	8	11

Baseline characteristics

Reporting groups

Reporting group title	Everolimus 10 mg + Exemestane 25 mg
Reporting group description: Everolimus (10 mg daily) with Exemestane (25 mg daily) (control arm).	
Reporting group title	Everolimus 10 mg
Reporting group description: Everolimus (10 mg daily) (investigational arm).	
Reporting group title	Capecitabine 1250 mg/m2
Reporting group description: Capecitabine (1250 mg/m2 twice daily) for two weeks, followed by one week rest period in 3-weeks cycles (investigational arm).	

Reporting group values	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m2
Number of subjects	104	103	102
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	65	64	69
From 65-84 years	38	38	33
85 years and over	1	1	0
Age Continuous Units: Years			
arithmetic mean	60.9	61.3	59.7
standard deviation	± 10.47	± 9.08	± 10.50
Sex: Female, Male Units: Participants			
Female	104	103	102
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	78	85	91
Black	1	2	0
Asian	11	8	8
Native American	3	2	0
Other	11	6	3
ECOG Performance Status Units: Subjects			
No Restrictions	54	48	57
Only Light Work	42	50	39
Only Self Care	5	3	4

Missing	3	2	2
---------	---	---	---

Reporting group values	Total		
Number of subjects	309		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	198		
From 65-84 years	109		
85 years and over	2		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	309		
Male	0		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	254		
Black	3		
Asian	27		
Native American	5		
Other	20		
ECOG Performance Status Units: Subjects			
No Restrictions	159		
Only Light Work	131		
Only Self Care	12		
Missing	7		

End points

End points reporting groups

Reporting group title	Everolimus 10 mg + Exemestane 25 mg
Reporting group description: Everolimus (10 mg daily) with Exemestane (25 mg daily) (control arm).	
Reporting group title	Everolimus 10 mg
Reporting group description: Everolimus (10 mg daily) (investigational arm).	
Reporting group title	Capecitabine 1250 mg/m2
Reporting group description: Capecitabine (1250 mg/m2 twice daily) for two weeks, followed by one week rest period in 3-weeks cycles (investigational arm).	
Reporting group title	Everolimus 10 mg + Exemestane 25 mg
Reporting group description: Everolimus (10 mg daily) with Exemestane (25 mg daily) (control arm).	
Reporting group title	Everolimus 10 mg
Reporting group description: Everolimus (10 mg daily) (investigational arm).	
Reporting group title	Capecitabine 1250 mg/m2
Reporting group description: Capecitabine (1250 mg/m2 twice daily) for two weeks, followed by one week rest period in 3-weeks cycles (investigational arm).	

Primary: Progression Free Survival (PFS) - Everolimus plus exemestane versus everolimus alone

End point title	Progression Free Survival (PFS) - Everolimus plus exemestane versus everolimus alone ^[1]
End point description: Progression Free Survival (PFS) is defined as the time from date of randomization to the date of first radiologically documented progression or death due to any cause. If a patient did not have an event, PFS was censored at the date of the last adequate tumor assessment. PFS was compared between the everolimus + exemestane combination therapy with the everolimus monotherapy.	
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 up to 39 months	

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: Primary endpoint "Progression Free Survival (PFS) - Everolimus plus exemestane versus everolimus alone" only apply to Treatment Arms: "Everolimus 10 mg + Exemestane 25 mg" and "Everolimus 10 mg"

End point values	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	103		
Units: Months				
median (confidence interval 90%)	8.41 (6.60 to 9.72)	6.77 (5.52 to 7.20)		

Statistical analyses

Statistical analysis title	PFS - Everolimus+exemestane vs everolimus alone
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Everolimus 10 mg
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.57
upper limit	0.97

Secondary: Progression Free Survival (PFS) - Everolimus plus exemestane versus Capecitabine alone

End point title	Progression Free Survival (PFS) - Everolimus plus exemestane versus Capecitabine alone ^[2]
-----------------	---

End point description:

Progression Free Survival (PFS) is defined as the time from date of randomization to the date of first radiologically documented progression or death due to any cause. If a patient did not have an event, PFS was censored at the date of the last adequate tumor assessment. PFS was compared between the everolimus + exemestane combination therapy with the everolimus monotherapy.

End point type	Secondary
----------------	-----------

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 up to 39 months

Notes:

[2] - 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: Primary endpoint "Progression Free Survival (PFS) - Everolimus plus exemestane versus Capecitabine alone" only apply to Treatment Arms: "Everolimus 10 mg + Exemestane 25 mg" and "Capecitabine 1250 mg/m2"

End point values	Everolimus 10 mg + Exemestane 25 mg	Capecitabine 1250 mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	102		
Units: Months				
median (confidence interval 90%)	8.41 (6.60 to 9.72)	9.59 (8.25 to 15.05)		

Statistical analyses

Statistical analysis title	PFS - Everolimus+exemestane vs Capecitabine alone
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Capecitabine 1250 mg/m2
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.66

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall Survival (OS) is defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died by the date of analysis cut-off, OS was censored at the date of last known date patient alive.	
End point type	Secondary
End point timeframe:	
Every 3 months following end of treatment visit, assessed for approximately 54 months	

End point values	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	103	102	
Units: Months				
median (confidence interval 90%)	23.06 (19.48 to 27.96)	29.27 (24.28 to 31.77)	25.56 (23.82 to 33.35)	

Statistical analyses

Statistical analysis title	OS - Everolimus+Exemestane vs Everolimus
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Everolimus 10 mg
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.7

Statistical analysis title	OS - Everolimus+Exemestane vs Capecitabine
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Capecitabine 1250 mg/m2
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.99
upper limit	1.79

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
-----------------	-----------------------------

End point description:

Overall Response Rate (ORR) as the proportion of patients whose best overall response is either complete response (CR) or partial response (PR) according to RECIST 1.1 This was assessed in the full patient population. Complete response is achieved when all lesions evaluated at baseline are absent at subsequent visit. Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR. Only descriptive statistics.

End point type	Secondary
----------------	-----------

End point timeframe:

From the date of randomization until the date of the first documented disease progression or date of death from any cause whichever came first, assessed for approximately 43 months

End point values	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	103	102	
Units: Percentage of Participants				
number (confidence interval 90%)	21 (13.9 to 27.8)	12 (6.9 to 18.2)	23 (15.9 to 30.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)
-----------------	-----------------------------

End point description:

Clinical Benefit Rate (CBR) is defined as the proportion of participants with a best overall response of complete response (CR) or partial response (PR) or stable disease (SD) or Non-CR/non-PD lasting more than 24 weeks based on local investigator's assessment according to RECIST 1.1. Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR, Stable disease (SD), neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD; CBR = CR+PR+SD. Only descriptive statistics.

End point type	Secondary
----------------	-----------

End point timeframe:

From the date of randomization until the date of the first documented disease progression or date of death from any cause whichever came first, assessed for approximately 43 months

End point values	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	103	102	
Units: Percentage of Participants				
number (confidence interval 90%)	59 (48.2 to 65.0)	43 (33.5 to 50.3)	53 (43.4 to 60.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 10% definitive deterioration in the global health status / Quality of life

End point title	Time to 10% definitive deterioration in the global health status / Quality of life
-----------------	--

End point description:

The global health status/QoL scale score of the QLQ-C30 is identified as the primary PRO variable of interest. Physical Functioning (PF), Emotional Functioning (EF) and Social Functioning (SF) scale scores of the QLQ-C30. The time to definitive 10% deterioration is the number of days between the date of randomization and the date of the assessment at which definitive deterioration is seen. Definitive 10% (5-point) deterioration is defined as a decrease in score by at least 10% (5-points) compared to baseline, with no later increase above this threshold observed during the course of the study.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, every 6 weeks up to about 43 months

End point values	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	103	102	
Units: Weeks				
median (confidence interval 90%)	30.86 (24.29 to 78.00)	23.86 (12.57 to 24.71)	61.29 (36.86 to 143.71)	

Statistical analyses

Statistical analysis title	QLQ-C30 Everolimus+Exemestane vs Everolimus
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Everolimus 10 mg
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.46
upper limit	0.88

Statistical analysis title	QLQ-C30 Everolimus+Exemestane vs Capecitabine
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Capecitabine 1250 mg/m2
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.93
upper limit	1.91

Secondary: Time to Eastern Cooperative Oncology Group (ECOG) performance deterioration

End point title	Time to Eastern Cooperative Oncology Group (ECOG) performance deterioration
-----------------	---

End point description:

The Eastern Cooperative Oncology Group (ECOG) Performance Status is a scale used to assess physical health of subjects, ranging from 0 (most active) to 5 (least active). Definitive deterioration is defined as no improvement in the ECOG status following observation of the deterioration.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, every 6 weeks up to about 43 months

End point values	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	103	102	
Units: Weeks				
median (confidence interval 90%)	72.57 (38.71 to 999)	126.57 (72.14 to 999)	120.00 (72.57 to 999)	

Statistical analyses

Statistical analysis title	ECOG - Everolimus+Exemestane vs Capecitabine
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Capecitabine 1250 mg/m2
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.78
upper limit	1.77

Statistical analysis title	ECOG - Everolimus+Exemestane vs Everolimus
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Everolimus 10 mg
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.72
upper limit	1.66

Secondary: Mean change in Treatment Satisfaction Questionnaire for Medication (TSQM) between week 3 and 12

End point title	Mean change in Treatment Satisfaction Questionnaire for Medication (TSQM) between week 3 and 12
End point description:	
TSQM was used to measure the Patients' self-reported satisfaction or dissatisfaction with the study treatment. The differences in mean scale scores between weeks 3 and 12 comparing treatment satisfaction in the different treatment arms: everolimus + exemestane combination therapy versus everolimus monotherapy, and everolimus + exemestane combination therapy versus capecitabine monotherapy. The TSQM version 1.4 domain scores range from 0 to 100 with higher scores representing a higher satisfaction on that domain.	
End point type	Secondary
End point timeframe:	
Week 3, Week 12	

End point values	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	103	102	
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Side-effects	-4.8 (± 28.88)	-9.1 (± 21.88)	-2.6 (± 22.45)	
Effectiveness	-2.2 (± 20.15)	1.2 (± 26.51)	1.2 (± 21.61)	
Convenience	-0.6 (± 12.00)	1.0 (± 16.41)	0.5 (± 17.67)	
Global satisfaction	-1.0 (± 17.32)	1.8 (± 20.80)	2.3 (± 16.96)	

Statistical analyses

Statistical analysis title	TSQM - Everolimus+Exemestane vs Everolimus
Statistical analysis description:	
Side-effects	

Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Everolimus 10 mg
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	4.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.3
upper limit	11.9

Statistical analysis title	TSQM - Everolimus+Exemestane vs Capecitabine
Statistical analysis description:	
Side-effects	
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Capecitabine 1250 mg/m2
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	-2.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.9
upper limit	5.5

Statistical analysis title	TSQM - Everolimus+Exemestane vs Everolimus
Statistical analysis description:	
Effectiveness	
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Everolimus 10 mg
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	-3.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.4
upper limit	3.8

Statistical analysis title	TSQM - Everolimus+Exemestane vs Capecitabine
-----------------------------------	--

Statistical analysis description:

Effectiveness

Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Capecitabine 1250 mg/m2
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	-3.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.7
upper limit	3

Statistical analysis title

TSQM - Everolimus+Exemestane vs Everolimus

Statistical analysis description:

Convenience

Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Everolimus 10 mg
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	-1.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.8
upper limit	2.5

Statistical analysis title

TSQM - Everolimus+Exemestane vs Capecitabine

Statistical analysis description:

Convenience

Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Capecitabine 1250 mg/m2
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	-1.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.5
upper limit	3.3

Statistical analysis title	TSQM - Everolimus+Exemestane vs Everolimus
Statistical analysis description:	
Global Satisfaction	
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Everolimus 10 mg
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	-2.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.3
upper limit	2.9

Statistical analysis title	TSQM - Everolimus+Exemestane vs Capecitabine
Statistical analysis description:	
Global Satisfaction	
Comparison groups	Everolimus 10 mg + Exemestane 25 mg v Capecitabine 1250 mg/m2
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	-3.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.4
upper limit	1.9

Post-hoc: All collected deaths

End point title	All collected deaths
End point description:	
On treatment deaths were collected from FPFT up to 30 days after study drug discontinuation, for a maximum duration of 224 weeks (treatment duration ranged from 1.3 to 220.0 weeks). Deaths post treatment survival follow up were collected after the on- treatment period, up to approximately 5 years. Patients who didn't die during the on-treatment period and had not stopped study participation at the time of data cut-off (end of study) were censored.	
End point type	Post-hoc
End point timeframe:	
up to 224 weeks (on-treatment), up to approximately 5 years (study duration)	

End point values	Everolimus 10 mg + Exemestane 25 mg	Everolimus 10 mg	Capecitabine 1250 mg/m2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	103	102	
Units: Participants				
On-treatment deaths	9	5	2	
Post-treatment deaths	62	55	57	
All deaths	71	60	59	

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	21.0
--------------------	------

Reporting groups

Reporting group title	Everolimus 10mg +@Exemestane 25mg
-----------------------	-----------------------------------

Reporting group description:

Everolimus 10mg +@Exemestane 25mg

Reporting group title	Everolimus 10mg
-----------------------	-----------------

Reporting group description:

Everolimus 10mg

Reporting group title	Capecitabine@1250mg/m2
-----------------------	------------------------

Reporting group description:

Capecitabine@1250mg/m2

Serious adverse events	Everolimus 10mg +@Exemestane 25mg	Everolimus 10mg	Capecitabine@1250 mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 104 (35.58%)	30 / 103 (29.13%)	30 / 102 (29.41%)
number of deaths (all causes)	9	5	2
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 104 (0.96%)	2 / 103 (1.94%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			

subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	4 / 102 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Drug intolerance			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	4 / 104 (3.85%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hernia			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	2 / 104 (1.92%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 104 (1.92%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial hyperreactivity			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 104 (1.92%)	2 / 103 (1.94%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	2 / 3	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hydrothorax			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 104 (0.96%)	1 / 103 (0.97%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 104 (1.92%)	3 / 103 (2.91%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	2 / 2	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 104 (1.92%)	1 / 103 (0.97%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 2	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 104 (0.96%)	3 / 103 (2.91%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 1	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood triglycerides increased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood uric acid increased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ilium fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	1 / 104 (0.96%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Headache			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 104 (1.92%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia	subjects affected / exposed	1 / 104 (0.96%)	3 / 103 (2.91%)	1 / 102 (0.98%)
	occurrences causally related to treatment / all	0 / 1	2 / 3	1 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia	subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia	subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia	subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia	subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia	subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders				
Vertigo positional	subjects affected / exposed	1 / 104 (0.96%)	1 / 103 (0.97%)	0 / 102 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders				
Diplopia	subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 104 (1.92%)	0 / 103 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 104 (0.96%)	2 / 103 (1.94%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	0 / 1	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 104 (2.88%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 104 (0.00%)	2 / 103 (1.94%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 104 (1.92%)	1 / 103 (0.97%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			

subjects affected / exposed	2 / 104 (1.92%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin toxicity			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 104 (2.88%)	4 / 103 (3.88%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	2 / 3	2 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 104 (1.92%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal chest pain			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial pyelonephritis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected cyst			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	8 / 104 (7.69%)	4 / 103 (3.88%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	3 / 8	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Urinary tract infection			
subjects affected / exposed	3 / 104 (2.88%)	1 / 103 (0.97%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 104 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 104 (0.96%)	1 / 103 (0.97%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			

subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 104 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Everolimus 10mg +@Exemestane 25mg	Everolimus 10mg	Capecitabine@1250 mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 104 (99.04%)	100 / 103 (97.09%)	99 / 102 (97.06%)
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 104 (14.42%)	8 / 103 (7.77%)	5 / 102 (4.90%)
occurrences (all)	17	9	6
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 104 (24.04%)	9 / 103 (8.74%)	24 / 102 (23.53%)
occurrences (all)	29	10	34
Fatigue			
subjects affected / exposed	39 / 104 (37.50%)	32 / 103 (31.07%)	34 / 102 (33.33%)
occurrences (all)	55	36	50
Non-cardiac chest pain			

subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6	4 / 103 (3.88%) 6	5 / 102 (4.90%) 6
Oedema peripheral subjects affected / exposed occurrences (all)	30 / 104 (28.85%) 35	22 / 103 (21.36%) 27	16 / 102 (15.69%) 22
Pyrexia subjects affected / exposed occurrences (all)	18 / 104 (17.31%) 38	12 / 103 (11.65%) 14	9 / 102 (8.82%) 10
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 7	1 / 103 (0.97%) 1	6 / 102 (5.88%) 7
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	37 / 104 (35.58%) 47	16 / 103 (15.53%) 20	18 / 102 (17.65%) 40
Dyspnoea subjects affected / exposed occurrences (all)	18 / 104 (17.31%) 21	19 / 103 (18.45%) 20	17 / 102 (16.67%) 19
Epistaxis subjects affected / exposed occurrences (all)	13 / 104 (12.50%) 13	11 / 103 (10.68%) 13	0 / 102 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 104 (3.85%) 4	7 / 103 (6.80%) 8	1 / 102 (0.98%) 1
Pleural effusion subjects affected / exposed occurrences (all)	4 / 104 (3.85%) 4	5 / 103 (4.85%) 6	6 / 102 (5.88%) 6
Pneumonitis subjects affected / exposed occurrences (all)	22 / 104 (21.15%) 27	21 / 103 (20.39%) 26	0 / 102 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6	2 / 103 (1.94%) 2	5 / 102 (4.90%) 6
Depression			

subjects affected / exposed occurrences (all)	8 / 104 (7.69%) 9	5 / 103 (4.85%) 5	5 / 102 (4.90%) 5
Insomnia subjects affected / exposed occurrences (all)	10 / 104 (9.62%) 10	8 / 103 (7.77%) 8	11 / 102 (10.78%) 12
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	16 / 104 (15.38%) 19	10 / 103 (9.71%) 12	6 / 102 (5.88%) 6
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	16 / 104 (15.38%) 21	14 / 103 (13.59%) 14	9 / 102 (8.82%) 9
Blood cholesterol increased subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 10	9 / 103 (8.74%) 12	1 / 102 (0.98%) 2
Blood creatinine increased subjects affected / exposed occurrences (all)	8 / 104 (7.69%) 11	6 / 103 (5.83%) 7	4 / 102 (3.92%) 4
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	15 / 104 (14.42%) 18	16 / 103 (15.53%) 18	2 / 102 (1.96%) 2
Platelet count decreased subjects affected / exposed occurrences (all)	8 / 104 (7.69%) 8	1 / 103 (0.97%) 2	1 / 102 (0.98%) 1
Weight decreased subjects affected / exposed occurrences (all)	31 / 104 (29.81%) 36	25 / 103 (24.27%) 27	15 / 102 (14.71%) 16
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	8 / 104 (7.69%) 8	9 / 103 (8.74%) 9	6 / 102 (5.88%) 6
Dysgeusia subjects affected / exposed occurrences (all)	17 / 104 (16.35%) 19	20 / 103 (19.42%) 20	14 / 102 (13.73%) 18
Headache			

subjects affected / exposed occurrences (all)	17 / 104 (16.35%) 19	16 / 103 (15.53%) 17	13 / 102 (12.75%) 18
Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1	1 / 103 (0.97%) 1	7 / 102 (6.86%) 7
Paraesthesia subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6	2 / 103 (1.94%) 3	3 / 102 (2.94%) 4
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	32 / 104 (30.77%) 41	26 / 103 (25.24%) 29	22 / 102 (21.57%) 25
Neutropenia subjects affected / exposed occurrences (all)	4 / 104 (3.85%) 4	4 / 103 (3.88%) 4	14 / 102 (13.73%) 15
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 104 (3.85%) 5	7 / 103 (6.80%) 9	3 / 102 (2.94%) 3
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	2 / 104 (1.92%) 2	1 / 103 (0.97%) 2	7 / 102 (6.86%) 8
Lacrimation increased subjects affected / exposed occurrences (all)	3 / 104 (2.88%) 3	4 / 103 (3.88%) 4	9 / 102 (8.82%) 9
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	10 / 104 (9.62%) 12	9 / 103 (8.74%) 9	13 / 102 (12.75%) 19
Abdominal pain upper subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6	3 / 103 (2.91%) 3	6 / 102 (5.88%) 12
Constipation subjects affected / exposed occurrences (all)	14 / 104 (13.46%) 16	15 / 103 (14.56%) 15	18 / 102 (17.65%) 23
Diarrhoea			

subjects affected / exposed	36 / 104 (34.62%)	34 / 103 (33.01%)	55 / 102 (53.92%)
occurrences (all)	61	46	104
Dry mouth			
subjects affected / exposed	10 / 104 (9.62%)	11 / 103 (10.68%)	12 / 102 (11.76%)
occurrences (all)	13	11	14
Dyspepsia			
subjects affected / exposed	8 / 104 (7.69%)	5 / 103 (4.85%)	7 / 102 (6.86%)
occurrences (all)	10	5	10
Mouth ulceration			
subjects affected / exposed	15 / 104 (14.42%)	13 / 103 (12.62%)	1 / 102 (0.98%)
occurrences (all)	21	17	3
Nausea			
subjects affected / exposed	35 / 104 (33.65%)	21 / 103 (20.39%)	52 / 102 (50.98%)
occurrences (all)	51	24	79
Stomatitis			
subjects affected / exposed	51 / 104 (49.04%)	45 / 103 (43.69%)	24 / 102 (23.53%)
occurrences (all)	87	61	30
Toothache			
subjects affected / exposed	5 / 104 (4.81%)	6 / 103 (5.83%)	1 / 102 (0.98%)
occurrences (all)	6	12	1
Vomiting			
subjects affected / exposed	20 / 104 (19.23%)	14 / 103 (13.59%)	29 / 102 (28.43%)
occurrences (all)	33	18	38
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 104 (5.77%)	3 / 103 (2.91%)	6 / 102 (5.88%)
occurrences (all)	6	3	8
Dermatitis acneiform			
subjects affected / exposed	7 / 104 (6.73%)	4 / 103 (3.88%)	0 / 102 (0.00%)
occurrences (all)	11	4	0
Dry skin			
subjects affected / exposed	11 / 104 (10.58%)	6 / 103 (5.83%)	14 / 102 (13.73%)
occurrences (all)	12	6	15
Erythema			
subjects affected / exposed	6 / 104 (5.77%)	4 / 103 (3.88%)	3 / 102 (2.94%)
occurrences (all)	7	7	4

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 104 (2.88%)	3 / 103 (2.91%)	62 / 102 (60.78%)
occurrences (all)	3	5	96
Pruritus			
subjects affected / exposed	11 / 104 (10.58%)	8 / 103 (7.77%)	7 / 102 (6.86%)
occurrences (all)	13	8	10
Rash			
subjects affected / exposed	22 / 104 (21.15%)	23 / 103 (22.33%)	12 / 102 (11.76%)
occurrences (all)	30	32	15
Skin hyperpigmentation			
subjects affected / exposed	1 / 104 (0.96%)	0 / 103 (0.00%)	6 / 102 (5.88%)
occurrences (all)	1	0	6
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	6 / 104 (5.77%)	1 / 103 (0.97%)	3 / 102 (2.94%)
occurrences (all)	6	1	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 104 (10.58%)	16 / 103 (15.53%)	13 / 102 (12.75%)
occurrences (all)	12	22	15
Back pain			
subjects affected / exposed	20 / 104 (19.23%)	8 / 103 (7.77%)	12 / 102 (11.76%)
occurrences (all)	21	9	15
Bone pain			
subjects affected / exposed	9 / 104 (8.65%)	4 / 103 (3.88%)	7 / 102 (6.86%)
occurrences (all)	13	4	9
Muscle spasms			
subjects affected / exposed	3 / 104 (2.88%)	6 / 103 (5.83%)	0 / 102 (0.00%)
occurrences (all)	4	6	0
Musculoskeletal chest pain			
subjects affected / exposed	10 / 104 (9.62%)	7 / 103 (6.80%)	8 / 102 (7.84%)
occurrences (all)	13	10	9
Musculoskeletal pain			
subjects affected / exposed	11 / 104 (10.58%)	5 / 103 (4.85%)	9 / 102 (8.82%)
occurrences (all)	11	5	10
Myalgia			

subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6	4 / 103 (3.88%) 4	3 / 102 (2.94%) 3
Neck pain subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6	1 / 103 (0.97%) 1	4 / 102 (3.92%) 4
Pain in extremity subjects affected / exposed occurrences (all)	14 / 104 (13.46%) 14	13 / 103 (12.62%) 15	16 / 102 (15.69%) 22
Infections and infestations			
Pneumonia subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 6	7 / 103 (6.80%) 12	2 / 102 (1.96%) 2
Rash pustular subjects affected / exposed occurrences (all)	6 / 104 (5.77%) 7	0 / 103 (0.00%) 0	0 / 102 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	8 / 104 (7.69%) 9	8 / 103 (7.77%) 11	5 / 102 (4.90%) 5
Urinary tract infection subjects affected / exposed occurrences (all)	12 / 104 (11.54%) 16	8 / 103 (7.77%) 11	5 / 102 (4.90%) 9
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	35 / 104 (33.65%) 42	32 / 103 (31.07%) 35	27 / 102 (26.47%) 34
Dehydration subjects affected / exposed occurrences (all)	9 / 104 (8.65%) 10	5 / 103 (4.85%) 6	5 / 102 (4.90%) 6
Hypercholesterolaemia subjects affected / exposed occurrences (all)	3 / 104 (2.88%) 3	9 / 103 (8.74%) 9	3 / 102 (2.94%) 3
Hyperglycaemia subjects affected / exposed occurrences (all)	13 / 104 (12.50%) 20	18 / 103 (17.48%) 25	8 / 102 (7.84%) 8
Hypertriglyceridaemia			

subjects affected / exposed	5 / 104 (4.81%)	15 / 103 (14.56%)	9 / 102 (8.82%)
occurrences (all)	8	17	9
Hypokalaemia			
subjects affected / exposed	11 / 104 (10.58%)	6 / 103 (5.83%)	5 / 102 (4.90%)
occurrences (all)	14	8	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2013	Amendment 1 was issued when four subjects were randomized, six subjects were in screening and one subject was discontinued due to disease progression. The main purpose of amendment 1 was to introduce the following changes: 1) A new exclusion criterion was added to exclude subjects who were being treated with sorivudine or its chemically related analogues (e.g. brivudine) or it was required to have at least 4 weeks period between end of treatment with such drugs and randomization date. 2) To be consistent with exclusion criterion 20 (re-numbered as 18 after amendment), which excluded subjects under coumarin-derivate anticoagulants, the exclusion criterion 15 was updated to also exclude subjects under low dose warfarin treatment. 3) Besides the pre-specified final OS analysis, it was desirable to assess the treatment effect on overall survival at the time of the pre-specified final PFS analysis. So this interim OS analysis was added in the amendment. No multiple testing considerations were needed because hypothesis testing was not part of either OS analysis.
16 June 2014	Amendment 2 was issued when 119 subjects were randomized. The main purpose of amendment 2 was to introduce the following change: • An interim analysis was added to allow early termination of the everolimus monotherapy arm when approximately 75 PFS events had been observed as per local tumor assessment, across the two arms: everolimus monotherapy and everolimus + exemestane combination arm. The intent of adding this interim analysis was to allow for the potential of early termination of the everolimus monotherapy arm, in case the efficacy in the everolimus monotherapy arm was far inferior to the everolimus + exemestane combination arm. This approach was endorsed by the Data Monitoring Committee (DMC) and Study Steering Committee.
18 April 2017	Amendment 3 was issued when study was fully recruited with 309 subjects, with the last subject randomized on 24-Nov-2014. Per initial protocol, the final PFS analysis was to be performed when at least 150 PFS events have been documented in 1) everolimus plus exemestane arm, and everolimus monotherapy arm, and 2) the everolimus plus exemestane arm, and capecitabine monotherapy arm. The OS analyses were to be conducted with two data cut-off dates; 2 years after the last subject's randomization and at the time of the final PFS analysis. Based on the observed 146 PFS events, there were 4 events less in one of the comparison, and there was a high risk of not reaching the events over extended time due to long lasting stable disease status in the remaining subjects. From the statistical perspective, loss of precision in the HR estimate with ≤ 4 events short of required 150 was considered minimal. In order to meet the regulatory commitment for submitting the CSR without affecting the scientific objective of the study, it was proposed in the protocol amendment 3 to: 1) Perform the final PFS analysis after approximately (instead of at least) 150 PFS events have been documented for each comparison. 2) Perform the final OS analysis at the same time as the final PFS analysis using the same data cut-off date. This amendment was considered "non-substantial" as it did not affect the subject management or the statistical analyses of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported