Clinical trial results:
An open-label, Phase II, single-arm study of everolimus in combination with letrozole in the treatment of postmenopausal women with estrogen receptor positive HER2 negative metastatic or locally advanced breast cancer

Summary

EudraCT number	2012-003065-17
Trial protocol	GB ES FR NL PT HU
Global end of trial date	13 January 2021

Results information

Result version number	v1
This version publication date	28 January 2022
First version publication date	28 January 2022

Trial information

Trial identification

Sponsor protocol code	CRAD001Y24135

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01698918
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	13 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate progression-free survival in patients treated with everolimus + letrozole in the first line setting

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	07 March 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	Argentina: 6
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Thailand: 13
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 52
Country: Number of subjects enrolled	Brazil: 21
Worldwide total number of subjects	202
EEA total number of subjects	65

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)	108
From 65 to 84 years	93
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted across 52 centers in 13 countries.

Pre-assignment

Screening details:

A total of 245 participants were screened of which 202 participants were enrolled in the this study to receive study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Everolimus+letrozole

Arm description:

Participants received everolimus in combination with letrozole as first line treatment.

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

Dosage and administration details:

Letrozole was self administered as a daily dose of 2.5mg continuously until disease progression or any other reason for which the patient might be discontinued. Everolimus in combination with letrozole was offered as the first line treatment.

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

Dosage and administration details:

Everolimus was self-administered as a daily dose of 10mg (two 5mg tablets) taken orally continuously until progression of disease, unacceptable toxicity or withdrawal of consent. Everolimus in combination with letrozole was offered as the first line treatment.

Arm title	Everolimus+exemestane

Arm description:

Participants who had disease progression in the first line setting (core phase) were offered second-line treatment (everolimus in combination with exemestane)

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

Dosage and administration details:

Exemestane was self administered as a daily dose of 25mg taken orally continuously until disease progression or any other reason for which the patient might be discontinued. Everolimus in combination

with exemestane was offered as the second-line treatment (participants who had disease progression in first line setting).

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

Dosage and administration details:

Everolimus was self-administered as a daily dose of 10mg (two 5mg tablets) taken orally continuously until progression of disease, unacceptable toxicity or withdrawal of consent. Everolimus in combination with exemestane was offered as the second-line treatment (participants who had disease progression in first line setting).

Number of subjects in period 1	Everolimus+letrozole	Everolimus+exemestane
Started	202	53
Completed	29	7
Not completed	173	46
Adverse event, serious fatal	2	1
Consent withdrawn by subject	11	1
Physician decision	7	3
Disease progression	120	38
Adverse event, non-fatal	33	3

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus+letrozole
Reporting group description:	
Participants received everolimus in combination with letrozole as first line treatment.	
Reporting group title	Everolimus+exemestane
Reporting group description:	
Participants who had disease progression in the first line setting (core phase) were offered second-line treatment (everolimus in combination with exemestane)	

Reporting group values	Everolimus+letrozole	Everolimus+exemestane	Total
Number of subjects	202	53	202
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)	108	37	108
From 65-84 years	93	16	93
85 years and over	1	0	1
Age Continuous Units: Years			
arithmetic mean	63.5	60.8	
standard deviation	± 8.75	± 8.90	-
Sex: Female, Male Units: Participants			
Female	202	53	202
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	146	32	146
Black	7	2	7
Asian	44	17	44
Pacific islander	1	1	1
Other	4	1	4

End points

End points reporting groups

Reporting group title	Everolimus+letrozole
Reporting group description:	
Participants received everolimus in combination with letrozole as first line treatment.	
Reporting group title	Everolimus+exemestane
Reporting group description:	
Participants who had disease progression in the first line setting (core phase) were offered second-line treatment (everolimus in combination with exemestane)	
Subject analysis set title	Everolimus+letrozole (first-line treatment)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received everolimus in combination with letrozole as first-line treatment	
Subject analysis set title	Everolimus+letrozole (first line treatment)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received everolimus in combination with letrozole as first-line treatment	
Subject analysis set title	Everolimus+exemestane (second line treatment)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who had disease progression in the first line setting (core phase) treated with second line treatment (everolimus in combination with exemestane)	
Subject analysis set title	Everolimus+exemestane (second-line treatment)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who had disease progression in the first line setting (core phase) treated with second-line treatment (everolimus in combination with exemestane)	
Subject analysis set title	Everolimus+letrozole (first-line treatment)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received everolimus in combination with letrozole as first-line treatment	
Subject analysis set title	Everolimus+letrozole (first line treatment)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received everolimus in combination with letrozole as first line treatment	
Subject analysis set title	Everolimus+letrozole (first line treatment)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received everolimus in combination with letrozole as first-line treatment	
Subject analysis set title	Everolimus+ letrozole (first-line treatment)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received everolimus in combination with letrozole as first-line treatment	
Subject analysis set title	Everolimus+letrozole (first-line treatment)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received everolimus in combination with letrozole as first-line treatment	
Subject analysis set title	Everolimus+letrozole (first-line treatment)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received everolimus in combination with letrozole as first-line treatment.

Subject analysis set title	Everolimus+exemestane (second-line treatment)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who had disease progression in the first line setting (core phase) treated with second-line treatment (everolimus in combination with exemestane)

Subject analysis set title	Everolimus+letrozole/exemestane
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received everolimus in combination with letrozole as first line treatment. Only participants who had disease progression in the first line setting (core phase) were offered second-line treatment (everolimus in combination with exemestane)

Primary: First-line treatment: Progression-free survival (PFS)

End point title	First-line treatment: Progression-free survival (PFS)[1]

End point description:

PFS in the first line setting is defined as the time from the date of enrollment to the date of first documented progression based on local radiology review or death due to any cause. If a participant did not progress or was not known to have died at the date of the analysis cut-off or start of another antineoplastic therapy, the PFS date was censored to the date of last adequate tumor assessment prior to cut-off date or start of antineoplastic therapy. The median PFS was estimated and presented along with 95% confidence intervals. The primary analysis of PFS for first line was performed 12 months after the last patient's recruitment.

End point type	Primary

End point timeframe:

From the date of enrollment to the date of first documented progression or deaths, assessed up to approximately 2.8 years

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 analyses were planned for the primary endpoint

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Months				
median (confidence interval 95%)	999 (18.0 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment: Overall response rate (ORR)

End point title	First-line treatment: Overall response rate (ORR)

End point description:

ORR in first line setting is defined as the percentage of participants while on first-line treatment with best overall response of complete response (CR) or partial response (PR) according to RECIST version 1.0 based on local review. Confidence intervals were calculated based on the Exact Clopper-Pearson method.
ORR while on first-line treatment was assessed up to 24 months after the last patient's recruitment.
CR: disappearance of all target lesions

PR: at least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters.

End point type	Secondary

End point timeframe:

From the date of enrollment up to approximately 3.8 years

End point values	Everolimus+letrozole (first line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Percentage of participants				
number (confidence interval 95%)	45.0 (38.1 to 52.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment: Clinical benefit rate (CBR)

End point title	First-line treatment: Clinical benefit rate (CBR)

End point description:

CBR in first line is defined as the percentage of participants while on first-line treatment with best overall response of CR, PR or stable disease (SD) with a duration of 24 weeks or longer, according to RECIST version 1.0 based on local review. Confidence intervals (CI) were calculated based on the Exact Clopper-Pearson method.
CBR while on first-line treatment was assessed up to 24 months after the last patient's recruitment.
CR: disappearance of all target lesions
PR: at least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters.
SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease

End point type	Secondary

End point timeframe:

From the date of enrollment up to approximately 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Percentage of participants				
number (confidence interval 95%)	74.3 (67.7 to 80.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Second-line treatment: Progression-free survival (PFS)

End point title	Second-line treatment: Progression-free survival (PFS)

End point description:

PFS in the second line setting is defined as the time interval between the start of the second-line treatment and documented disease progression based on local radiology review or death due to any cause reported during or after second-line treatment period. If a participant did not progress or was not known to have died at the date of the analysis cut-off or start of another antineoplastic therapy, the PFS date was censored to the date of last adequate tumor assessment prior to cut-off date or start of antineoplastic therapy. The median PFS was estimated and presented along with 95% confidence intervals.
PFS while on second-line treatment was assessed up to 24 months after the last patient's recruitment.

End point type	Secondary

End point timeframe:

From the start of the second-line treatment to the date of first documented progression or death, assessed up to approximately 2.4 years

End point values	Everolimus+exemestane (second line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Months				
median (confidence interval 95%)	3.7 (1.9 to 7.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Second-line treatment: Overall response rate (ORR)

End point title	Second-line treatment: Overall response rate (ORR)

End point description:

ORR in second line is defined as the percentage of participants receiving second-line study treatment with best overall response of complete response (CR) or partial response (PR) according to RECIST version 1.0 based on local review. Confidence intervals (CI) were calculated based on the Exact Clopper-Pearson method.
ORR while on second-line treatment was assessed up to 24 months after the last patient's recruitment.
CR: disappearance of all target lesions
PR: at least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters

End point type	Secondary

End point timeframe:

From the start of the second-line treatment up to approximately 2.4 years

End point values	Everolimus+exemestane (second-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Percentage of participants				
number (confidence interval 95%)	6.0 (1.3 to 16.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Second-line treatment: Clinical benefit rate (CBR)

End point title	Second-line treatment: Clinical benefit rate (CBR)

End point description:

CBR in second line is defined as the percentage of participants receiving second-line study treatment with best overall response of CR, PR or stable disease (SD) with a duration of 24 weeks or longer, according to RECIST version 1.0 based on local review. Confidence intervals (CI) were calculated based on the Exact Clopper-Pearson method.
CBR while on second-line treatment was assessed up to 24 months after the last patient's recruitment.
CR: disappearance of all target lesions
PR: at least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters.
SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease

End point type	Secondary

End point timeframe:

From the start of the second-line treatment up to approximately 2.4 years

End point values	Everolimus+exemestane (second-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Percentage of participants				
number (confidence interval 95%)	28.0 (16.2 to 42.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS following first-line treatment with everolimus + letrozole is defined as the time from the date of

receiving first line study treatment to date of death due to any cause (including first-line and second-line treatment periods). If a participant was not known to have died, survival was censored at the date of last contact.
OS following first-line treatment was assessed up to 24 months after last patient's recruitment.

End point type	Secondary

End point timeframe:

From the date of receiving first-line study treatment to date of death, assessed up to approximately 3.8 years

End point values	Everolimus+letrozole/exemestane			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Months				
median (confidence interval 95%)	999 (37.0 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment: Time to first stomatitis episode as assessed by the Oral Stomatitis Daily Questionnaire (OSDQ)

End point title	First-line treatment: Time to first stomatitis episode as assessed by the Oral Stomatitis Daily Questionnaire (OSDQ)

End point description:

The time to first occurrence of stomatitis based on OSDQ is defined as time from first-line treatment administration to start date of the stomatitis episode recorded in the OSDQ in the first line. The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The first item asked the participants when they experienced the first symptoms of stomatitis. Start date of the first occurrence of stomatitis is defined as the first date ever recorded for this item in the questionnaire. Patient reported outcomes (PROs) were assessed up to 24 months after last patient's recruitment.

End point type	Secondary

End point timeframe:

From first-line treatment administration until first stomatitis episode in the first line, assessed up to approximately 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Weeks				
median (confidence interval 95%)	1.7 (1.3 to 2.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment: Duration of first stomatitis based on OSDQ

End point title	First-line treatment: Duration of first stomatitis based on OSDQ

End point description:

The duration of the first stomatitis episode was calculated using the start and end date recorded in the OSDQ. The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis. The first item of the questionnaire asked the participants the date when they experienced the first symptoms of stomatitis. Start date of the first occurrence of stomatitis is defined as the first date ever recorded for this item in the questionnaire. Stop date of the first stomatitis episode is defined as the last date the OSDQ was completed for this episode. Participants were censored if they died before resolution of stomatitis, received a new anticancer therapy, discontinued the study treatment with no resolution of the stomatitis or the stomatitis event was still on-going at the cut-off. PROs were assessed up to 24 months after last patient's recruitment.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode in first line until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Weeks				
median (confidence interval 95%)	12.3 (4.1 to 23.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment: Number of participants with shift of response in OSDQ score on overall health at the end of the first stomatitis episode

End point title	First-line treatment: Number of participants with shift of response in OSDQ score on overall health at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily up to the resolution of the stomatitis episode. The second item asked the participant to rate their overall health from 0 (worst possible) to 10 (perfect health). The overall health OSDQ scores are presented as the shift from Day 1 of first stomatitis episode value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded.

End of first stomatitis value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Participants				
From 0 to 0	2			
From 0 to 1	1			
From 0 to 5	1			
From 1 to 1	1			
From 1 to 2	1			
From 2 to 5	1			
From 2 to 8	2			
From 3 to 0	1			
From 3 to 3	3			
From 3 to 5	2			
From 3 to 10	2			
From 4 to 3	2			
From 4 to 5	1			
From 4 to 7	1			
From 4 to 8	2			
From 5 to 0	1			
From 5 to 3	3			
From 5 to 4	1			
From 5 to 5	7			
From 5 to 6	4			
From 5 to 7	3			
From 5 to 9	1			
From 5 to 10	2			
From 6 to 5	2			
From 6 to 6	3			
From 6 to 7	2			
From 6 to 9	2			
From 7 to 3	2			
From 7 to 4	1			
From 7 to 5	1			
From 7 to 7	3			
From 7 to 9	1			
From 8 to 1	1			
From 8 to 7	1			
From 8 to 8	4			
From 8 to 9	5			
From 8 to 10	2			
From 9 to 0	1			

From 9 to 4	2			
From 9 to 8	1			
From 9 to 9	8			
From 10 to 3	1			
From 10 to 9	1			
From missing value to missing value	3			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment: Number of participants with shift of response in OSDQ score on mouth and throat soreness at the end of the first stomatitis episode

End point title	First-line treatment: Number of participants with shift of response in OSDQ score on mouth and throat soreness at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The third item asked the participant to rate their mouth and throat soreness from 0 (no soreness) to 4 (extreme soreness). The mouth and throat soreness OSDQ scores are presented as the shift from Day 1 of first stomatitis episode value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded. End of first stomatitis value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Participants				
From 0 to 0	3			
From 1 to 0	22			
From 1 to 1	12			
From 1 to 2	3			
From 2 to 0	13			
From 2 to 1	7			
From 2 to 2	4			
From 2 to 3	1			
From 3 to 0	9			
From 3 to 1	4			
From 3 to 2	5			
From 3 to 3	1			
From 3 to 4	1			
From 4 to 1	2			
From 4 to 2	1			

From missing value to missing value	4			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment: Number of participants with shift of response in OSDQ score on mouth and throat soreness limiting swallowing, drinking, eating, talking and sleeping at the end of the first stomatitis episode

End point title	First-line treatment: Number of participants with shift of response in OSDQ score on mouth and throat soreness limiting swallowing, drinking, eating, talking and sleeping at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The fourth item asked the participant to rate how much their mouth and throat soreness limited them in 1) swallowing, 2) drinking, 3) eating, 4) talking and 5) sleeping. For each activity, mouth and throat soreness scores ranged from 0 (not limited) to 4 (unable to do). Scores are presented as the shift from Day 1 of first stomatitis episode value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded. End of first stomatitis value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Participants				
Swallowing: From 0 to 0	40			
Swallowing: From 0 to 1	3			
Swallowing: From 0 to 2	1			
Swallowing: From 1 to 0	7			
Swallowing: From 1 to 1	6			
Swallowing: From 1 to 2	3			
Swallowing: From 1 to 3	1			
Swallowing: From 2 to 0	6			
Swallowing: From 2 to 1	4			
Swallowing: From 2 to 2	2			
Swallowing: From 3 to 0	8			
Swallowing: From 3 to 1	2			
Swallowing: From 3 to 3	2			
Swallowing: From missing value to missing value	7			
Drinking: From 0 to 0	48			

Drinking: From 0 to 1	4			
Drinking: From 0 to 2	1			
Drinking: From 1 to 0	10			
Drinking: From 1 to 1	5			
Drinking: From 1 to 2	1			
Drinking: From 2 to 0	4			
Drinking: From 2 to 1	3			
Drinking: From 2 to 2	3			
Drinking: From 2 to 3	2			
Drinking: From 3 to 0	6			
Drinking: From 3 to 1	1			
Drinking: From 3 to 3	1			
Drinking: From missing value to missing value	9			
Eating: From 0 to 0	17			
Eating: From 0 to 1	2			
Eating: From 0 to 2	1			
Eating: From 1 to 0	14			
Eating: From 1 to 1	11			
Eating: From 1 to 2	2			
Eating: From 2 to 0	8			
Eating: From 2 to 1	3			
Eating: From 2 to 2	4			
Eating: From 2 to 3	2			
Eating: From 3 to 0	7			
Eating: From 3 to 1	6			
Eating: From 3 to 2	3			
Eating: From 3 to 3	4			
Eating: From 4 to 1	1			
Eating: From missing value to missing value	7			
Talking: From 0 to 0	45			
Talking: From 0 to 1	5			
Talking: From 1 to 0	12			
Talking: From 1 to 1	2			
Talking: From 2 to 0	5			
Talking: From 2 to 1	2			
Talking: From 2 to 2	3			
Talking: From 2 to 3	1			
Talking: From 3 to 0	4			
Talking: From 3 to 2	1			
Talking: From 3 to 3	3			
Talking: From missing value to missing value	9			
Sleeping: From 0 to 0	48			
Sleeping: From 0 to 1	4			
Sleeping: From 0 to 2	1			
Sleeping: From 1 to 0	8			
Sleeping: From 1 to 1	2			
Sleeping: From 1 to 2	2			
Sleeping: From 2 to 0	4			
Sleeping: From 2 to 1	3			
Sleeping: From 2 to 2	6			

Sleeping: From 3 to 0	1			
Sleeping: From 3 to 1	1			
Sleeping: From 3 to 2	1			
Sleeping: From missing value to missing value	11			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment: Number of participants with shift of response in OSDQ score on mouth pain severity at the end of the first stomatitis episode

End point title	First-line treatment: Number of participants with shift of response in OSDQ score on mouth pain severity at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The fifth item asked the participant to rate their mouth pain severity from 0 (no pain) to 10 (unbearable pain). The mouth pain severity OSDQ scores are presented as the shift from Day 1 of first stomatitis episode value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded. End of first stomatitis value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Participants				
From 0 to 0	5			
From 1 to 0	10			
From 1 to 1	6			
From 1 to 2	1			
From 1 to 3	1			
From 1 to 5	1			
From 2 to 0	6			
From 2 to 3	1			
From 3 to 0	7			
From 3 to 1	1			
From 3 to 2	2			
From 3 to 3	1			
From 3 to 4	2			
From 4 to 0	4			
From 4 to 1	2			
From 4 to 4	1			
From 4 to 5	1			

From 5 to 0	3			
From 5 to 1	1			
From 5 to 2	1			
From 5 to 3	1			
From 5 to 4	1			
From 5 to 5	1			
From 5 to 6	1			
From 5 to 7	1			
From 5 to 10	1			
From 6 to 0	2			
From 6 to 1	1			
From 6 to 2	1			
From 6 to 5	1			
From 6 to 6	1			
From 6 to 8	1			
From 7 to 0	2			
From 7 to 1	2			
From 7 to 2	1			
From 7 to 7	1			
From 8 to 0	3			
From 8 to 2	1			
From 8 to 4	2			
From 8 to 5	1			
From 8 to 6	1			
From 8 to 9	1			
From 9 to 0	2			
From 9 to 9	1			
From missing value to missing value	4			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment: Number of participants with shift of response in OSDQ score on mouth pain severity affecting daily activities at the end of the first stomatitis episode

End point title	First-line treatment: Number of participants with shift of response in OSDQ score on mouth pain severity affecting daily activities at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The sixth item asked the participant to rate their mouth pain severity affecting daily activities score from 0 (no effect on daily activities) to 10 (completely prevented from doing daily activities). The mouth pain severity affecting daily activities OSDQ scores are presented as the shift from Day 1 of first stomatitis episode value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded. End of first stomatitis value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Participants				
From 0 to 0	33			
From 0 to 1	1			
From 0 to 5	1			
From 1 to 0	7			
From 1 to 1	4			
From 1 to 4	2			
From 2 to 0	6			
From 2 to 1	1			
From 2 to 2	3			
From 2 to 3	1			
From 2 to 4	1			
From 3 to 0	3			
From 3 to 1	3			
From 3 to 2	1			
From 3 to 3	1			
From 3 to 4	1			
From 4 to 0	2			
From 5 to 0	2			
From 5 to 1	1			
From 5 to 2	1			
From 5 to 3	1			
From 5 to 5	1			
From 5 to 6	1			
From 6 to 1	1			
From 6 to 5	1			
From 6 to 8	1			
From 7 to 0	1			
From 8 to 0	1			
From 8 (to 8	1			
From 8 to 10	1			
From 9 to 0	1			
From 9 to 8	1			
From 10 to 10	1			
From missing value to missing value	4			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment (stomatitis sub-study): Time to first stomatitis

episode as assessed by the OSDQ

End point title	First-line treatment (stomatitis sub-study): Time to first stomatitis episode as assessed by the OSDQ

End point description:

The time to first occurrence of stomatitis based on OSDQ is defined as time from first study treatment administration in the first line to start date of the first stomatitis episode recorded in the OSDQ. The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The first item asked the participants when they experienced the first symptoms of stomatitis. Start date of the first occurrence of stomatitis is defined as the first date ever recorded for this item in the questionnaire. PROs were assessed up to 24 months after last patient's recruitment.
Only participants who were randomized in the stomatitis sub-study were included in this analysis.

End point type	Secondary

End point timeframe:

From first study treatment administration in the first line until first stomatitis episode, assessed up to approximately 3.8 years

End point values	Everolimus+ letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Weeks				
median (confidence interval 95%)				
Dexamethasone	1.4 (0.9 to 1.9)			
Standard of care	2.3 (0.7 to 5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment (stomatitis sub-study): Duration of first stomatitis based on OSDQ

End point title	First-line treatment (stomatitis sub-study): Duration of first stomatitis based on OSDQ

End point description:

The duration of the first stomatitis was calculated using the start and end date reported in the OSDQ. The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis. The first item asked the participants the date when they experienced the first symptoms of stomatitis. Start date of the first stomatitis is defined as the first date ever recorded for this item in the questionnaire. Stop date of the first stomatitis is defined as the last date the OSDQ was completed for this episode. Participants were censored if they died before resolution of stomatitis, received a new anticancer therapy, discontinued the study treatment with no resolution of the stomatitis or the stomatitis was still on-going at the cut-off. PROs were assessed up to 24 months after last patient's recruitment. Only participants who were randomized in the stomatitis sub-study were included in this analysis.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Weeks				
median (confidence interval 95%)				
Dexamethasone	999 (999 to 999)			
Standard of Care	13.7 (1.4 to 13.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on overall health at the end of the first stomatitis episode

End point title	First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on overall health at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The second item asked the participant to rate their overall health from 0 (worst possible) to 10 (perfect health). The overall health OSDQ score are presented as the shift from Day 1 of first stomatitis episode value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded. End of first stomatitis value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.
Only participants who were randomized in the stomatitis sub-study were included in this analysis.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Participants				
Dexamethasone: From 2 to 5	1			
Dexamethasone: From 4 to 3	1			
Dexamethasone: From 5 to 5	1			
Dexamethasone: From 5 to 6	1			
Dexamethasone: From 5 to 7	1			
Dexamethasone: From 6 to 5	1			

Dexamethasone: From 6 to 7	1			
Dexamethasone: From 7 to 3	1			
Dexamethasone: From 8 to 8	1			
Dexamethasone: From 8 to 9	1			
Dexamethasone: From 9 to 9	1			
SoC: From 0 to 5	1			
SoC: From 4 to 3	1			
SoC: From 4 to 8	1			
SoC: From 5 to 5	1			
SoC: From 6 to 7	1			
SoC: From 7 to 3	1			
SoC: From 8 to 9	1			
SoC: From 8 to 10	1			
SoC: From 9 to 4	1			
SoC: From 9 to 9	2			
SoC: From missing value to missing value	2			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on mouth and throat soreness at the end of the first stomatitis episode

End point title	First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on mouth and throat soreness at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The third item asked the participant to rate their mouth and throat soreness from 0 (no soreness) to 4 (extreme soreness). The mouth and throat soreness OSDQ scores are presented as the shift from Day 1 of first stomatitis episode value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded. End of first stomatitis value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.
Only participants who were randomized in the stomatitis sub-study were included in this analysis.

End point type	Secondary

End point timeframe:

From start date of stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Participants				
Dexamethasone: From 0 to 0	1			
Dexamethasone: From 1 to 0	3			
Dexamethasone: From 1 to 1	2			

Dexamethasone: From 2 to 0	1			
Dexamethasone: From 2 to 1	3			
Dexamethasone: From 3 to 1	1			
SoC: From 1 to 0	1			
SoC: From 1 to 1	1			
SoC: From 2 to 1	1			
SoC: From 3 to 0	2			
SoC: From 3 to 1	1			
SoC: From 3 to 2	3			
SoC: From 4 to 1	1			
SoC: From 4 to 2	1			
SoC: From missing value to missing value	2			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on mouth and throat soreness limiting swallowing, drinking, eating, talking and sleeping at the end of the first stomatitis episode

End point title	First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on mouth and throat soreness limiting swallowing, drinking, eating, talking and sleeping at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The fourth item asked the participant to rate how much their mouth and throat soreness limited them in 1) swallowing, 2) drinking, 3) eating, 4) talking and 5) sleeping. For each activity, mouth and throat soreness scores ranged from 0 (not limited) to 4 (unable to do). Scores are presented as the shift from Day 1 of first stomatitis stomatitis value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded. End of first episode value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.
Only participants who were randomized in the stomatitis sub-study were included in this analysis.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Participants				
Swallowing (dexamethasone): From 0 to 0	6			
Swallowing (dexamethasone): From 1 to 0	2			
Swallowing (dexamethasone): From 1 to 2	1			

Swallowing (dexamethasone): From 2 to 0	1			
Swallowing (dexamethasone): From 2 to 2	1			
Swallowing (SoC): From 0 to 0	5			
Swallowing (SoC): From 1 to 2	1			
Swallowing (SoC): From 2 to 0	1			
Swallowing (SoC): From 2 to 1	2			
Swallowing (SoC): From 3 to 0	1			
Swallowing (SoC): From 3 to 1	1			
Swallowing(SoC)From missing value to missing value	2			
Drinking (dexamethasone): From 0 to 0	6			
Drinking (dexamethasone): From 1 to 0	2			
Drinking (dexamethasone): From 1 to 1	1			
Drinking (dexamethasone): From 2 to 0	1			
Drinking (dexamethasone): From 2 to 2	1			
Drinking (SoC): From 0 to 0	3			
Drinking (SoC): From 0 to 1	2			
Drinking (SoC): From 2 to 0	3			
Drinking (SoC): From 2 to 1	1			
Drinking (SoC): From 3 to 0	1			
Drinking (SoC): From 3 to 1	1			
Drinking(SoC):From missing value to missing value	2			
Eating (dexamethasone): From 0 to 0	3			
Eating (dexamethasone): From 1 to 0	1			
Eating (dexamethasone): From 1 to 1	2			
Eating (dexamethasone): From 2 to 0	1			
Eating (dexamethasone): From 2 to 1	2			
Eating (dexamethasone): From 2 to 2	1			
Eating (dexamethasone): From 3 to 1	1			
Eating (SoC): From 1 to 0	2			
Eating (SoC): From 1 to 1	1			
Eating (SoC): From 2 to 0	1			
Eating (SoC): From 3 to 0	1			
Eating (SoC): From 3 to 1	2			
Eating (SoC): From 3 to 2	3			
Eating (SoC): From 4 to 1	1			
Eating (SoC): From missing value to missing value	2			
Talking (dexamethasone): From 0 to 0	6			
Talking (dexamethasone): From 1 to 0	1			
Talking (dexamethasone): From 2 to 0	2			
Talking (dexamethasone): From 2 to 1	1			
Talking (dexamethasone): From 2 to 2	1			
Talking (SoC): From 0 to 0	5			
Talking (SoC): From 0 to 1	1			
Talking (SoC): From 1 to 0	1			
Talking (SoC): From 2 to 0	1			
Talking (SoC): From 2 to 1	1			
Talking (SoC): From 3 to 0	1			
Talking (SoC): From 3 to 2	1			

Talking (SoC): From missing value to missing value	2			
Sleeping (dexamethasone): From 0 to 0	7			
Sleeping (dexamethasone): From 1 to 0	1			
Sleeping (dexamethasone): From 2 to 0	1			
Sleeping (dexamethasone): From 2 to 1	1			
Sleeping (dexamethasone): From 2 to 2	1			
Sleeping (SoC): From 0 to 0	5			
Sleeping (SoC): From 0 to 2	1			
Sleeping (SoC): From 1 to 1	1			
Sleeping (SoC): From 2 to 0	2			
Sleeping (SoC): From 3 to 0	1			
Sleeping (SoC): From 3 to 1	1			
Sleeping(SoC):From missing value to missing value	2			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on mouth pain severity at the end of the first stomatitis episode

End point title	First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on mouth pain severity at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The fifth item asked the participant to rate their mouth pain severity from 0 (no pain) to 10 (unbearable pain). The mouth pain severity OSDQ scores are presented as the shift from Day 1 of first stomatitis episode value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded. End of first stomatitis value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.
Only participants who were randomized in the stomatitis sub-study were included in this analysis.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Participants				
Dexamethasone: From 0 to 0	1			
Dexamethasone: From 1 to 2	1			
Dexamethasone: From 2 to 0	2			
Dexamethasone: From 3 to 0	2			
Dexamethasone: From 3 to 1	1			

Dexamethasone: From 3 to 2	1			
Dexamethasone: From 5 to 2	1			
Dexamethasone: From 5 to 3	1			
Dexamethasone: From 7 to 1	1			
SoC: From 1 to 0	1			
SoC: From 1 to 1	1			
SoC: From 4 to 1	2			
SoC: From 5 to 5	1			
SoC: From 7 to 0	1			
SoC: From 8 to 2	1			
SoC: From 8 to 4	2			
SoC: From 8 to 6	1			
SoC: From 9 to 0	1			
SoC: From missing value to missing value	2			

Statistical analyses

No statistical analyses for this end point

Secondary: First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on mouth pain severity affecting daily activities at the end of the first stomatitis episode

End point title	First-line treatment (stomatitis sub-study): Number of participants with shift of response in OSDQ score on mouth pain severity affecting daily activities at the end of the first stomatitis episode

End point description:

The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Participants completed the questionnaire daily until the resolution of the stomatitis episode. The sixth item asked the participant to rate their mouth pain severity affecting daily activities score from 0 (no effect on daily activities) to 10 (completely prevented from doing daily activities). The mouth pain severity affecting daily activities OSDQ scores are presented as the shift from Day 1 of first stomatitis episode value to the value at the end of the first episode of stomatitis. Day 1 is defined as the first OSDQ questionnaire recorded. End of first stomatitis value is defined as the last OSDQ questionnaire of the first episode of stomatitis. PROs were assessed up to 24 months after last patient's recruitment.
Only participants who were randomized in the stomatitis sub-study were included in this analysis.

End point type	Secondary

End point timeframe:

From start date of first stomatitis episode until its resolution, assessed up to 3.8 years

End point values	Everolimus+letrozole (first-line treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Participants				
Dexamethasone: From 0 to 0	5			
Dexamethasone: From 1 to 0	1			
Dexamethasone: From 2 to 0	2			
Dexamethasone: From 3 to 2	1			

Dexamethasone: From 5 to 3	1			
Dexamethasone: From 6 to 1	1			
SoC: From 0 to 0	4			
SoC: From 1 to 4	1			
SoC: From 2 to 2	1			
SoC: From 3 to 0	1			
SoC: From 3 to 1	1			
SoC: From 5 to 2	1			
SoC: From 5 to 5	1			
SoC: From 9 to 0	1			
SoC: From missing value to missing value	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical benfit during extension phase

End point title	Number of participants with clinical benfit during extension phase

End point description:

Number of participants with clinical benefit as judged by the investigator during the extension phase. The extension phase for up to 3 years for participants who were continuing to benefit from study treatment following the end of the core study phase (24 months after last patient's recruitment) was added in the amendment 5 (dated 14-Feb-2017). Results are presented by line of treatment

End point type	Secondary

End point timeframe:

From the end of core phase (upon approval of amendment 5) up to approximately 3 years

End point values	Everolimus+letrozole (first-line treatment)	Everolimus+exemestane (second-line treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	202	53		
Units: Participants				
Extension Week 1	34	6		
Extension Week 12	30	5		
Extension Week 24	28	4		
Extension Week 36	23	3		
Extension Week 48	20	3		
Extension Week 60	18	3		
Extension Week 72	16	3		
Extension Week 84	13	3		
Extension Week 96	12	3		
Extension Week 108	12	3		
Extension Week 120	11	2		
Extension Week 132	10	1		
Extension Week 144	8	1		

Extension End of treatment	11	1		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths

End point description:

On-treatment deaths in first line were collected from first dose of first-line treatment until the date of last administration of the first-line study treatment plus 28 days for participants not entering second-line or the minimum between the date of last administration of the first-line study treatment plus 28 days and the date of first administration of second-line study treatment minus one day for participants entering second line, up to 7.3 years.
On-treatment deaths in second line were collected from first dose of second-line treatment to 28 days after the last administration of second-line treatment, up to 5.4 years.
Total deaths were collected from first dose of first-line treatment until the end of study, up to 7.3 years

End point type	Post-hoc

End point timeframe:

On-treatment deaths (first line): Up to 7.3 years. On-treatment deaths (second line): Up to 5.4 years. Total deaths: Up to 7.3 years

End point values	Everolimus+letrozole/exemestane			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Participants				
On -treatment deaths in first line	11			
On-treatment deaths in second line	2			
Total deaths	62			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First line: from first dose of first-line treatment up to 7.3 years
Second line: from first dose of second-line treatment up to 5.4 years

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	20.1

Reporting groups

Reporting group title	Everolimus + Letrozole

Reporting group description:

Participants received everolimus in combination with letrozole as first-line treatment.

Reporting group title	Everolimus + Exemestane

Reporting group description:

Participants who had disease progression in the first line setting (core phase) were treated with second-line treatment (everolimus in combination with exemestane)

Serious adverse events	Everolimus + Letrozole	Everolimus + Exemestane	
Total subjects affected by serious adverse events			
subjects affected / exposed	72 / 202 (35.64%)	8 / 53 (15.09%)	
number of deaths (all causes)	11	2	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			

subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			

subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Urogenital prolapse			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchostenosis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 202 (2.97%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	3 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			

subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	4 / 202 (1.98%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 202 (1.49%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 202 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 202 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 202 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accident			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	1 / 202 (0.50%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Snake bite			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	4 / 202 (1.98%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Palpitations			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			

subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 202 (2.48%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	3 / 202 (1.49%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pupils unequal			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 202 (0.50%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 202 (1.49%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	5 / 202 (2.48%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 202 (1.98%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 202 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			

subjects affected / exposed	0 / 202 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocyturia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 202 (0.50%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	5 / 202 (2.48%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 202 (1.98%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	0 / 202 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	9 / 202 (4.46%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	5 / 11	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 202 (0.50%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Soft tissue infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 202 (0.99%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	3 / 202 (1.49%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Everolimus + Letrozole	Everolimus + Exemestane	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	202 / 202 (100.00%)	46 / 53 (86.79%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	42 / 202 (20.79%)	5 / 53 (9.43%)	
occurrences (all)	58	6	
Alanine aminotransferase increased			
subjects affected / exposed	36 / 202 (17.82%)	5 / 53 (9.43%)	
occurrences (all)	48	5	
Blood cholesterol increased			
subjects affected / exposed	42 / 202 (20.79%)	0 / 53 (0.00%)	
occurrences (all)	71	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	21 / 202 (10.40%)	7 / 53 (13.21%)	
occurrences (all)	52	10	
Blood creatinine increased			
subjects affected / exposed	18 / 202 (8.91%)	3 / 53 (5.66%)	
occurrences (all)	31	7	
Weight decreased			
subjects affected / exposed	91 / 202 (45.05%)	15 / 53 (28.30%)	
occurrences (all)	104	18	
Gamma-glutamyltransferase increased			

subjects affected / exposed	5 / 202 (2.48%)	3 / 53 (5.66%)	
occurrences (all)	5	3	
White blood cell count decreased			
subjects affected / exposed	9 / 202 (4.46%)	3 / 53 (5.66%)	
occurrences (all)	26	5	
Vascular disorders			
Hot flush			
subjects affected / exposed	15 / 202 (7.43%)	1 / 53 (1.89%)	
occurrences (all)	19	1	
Hypertension			
subjects affected / exposed	50 / 202 (24.75%)	9 / 53 (16.98%)	
occurrences (all)	66	13	
Lymphoedema			
subjects affected / exposed	18 / 202 (8.91%)	1 / 53 (1.89%)	
occurrences (all)	19	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 202 (9.41%)	1 / 53 (1.89%)	
occurrences (all)	26	1	
Dysgeusia			
subjects affected / exposed	32 / 202 (15.84%)	1 / 53 (1.89%)	
occurrences (all)	33	1	
Headache			
subjects affected / exposed	34 / 202 (16.83%)	4 / 53 (7.55%)	
occurrences (all)	55	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	71 / 202 (35.15%)	11 / 53 (20.75%)	
occurrences (all)	158	13	
Neutropenia			
subjects affected / exposed	15 / 202 (7.43%)	1 / 53 (1.89%)	
occurrences (all)	28	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	32 / 202 (15.84%)	2 / 53 (3.77%)	
occurrences (all)	46	3	

Fatigue			
subjects affected / exposed	70 / 202 (34.65%)	5 / 53 (9.43%)	
occurrences (all)	96	5	
Influenza like illness			
subjects affected / exposed	7 / 202 (3.47%)	3 / 53 (5.66%)	
occurrences (all)	10	3	
Oedema peripheral			
subjects affected / exposed	63 / 202 (31.19%)	6 / 53 (11.32%)	
occurrences (all)	104	7	
Pyrexia			
subjects affected / exposed	37 / 202 (18.32%)	3 / 53 (5.66%)	
occurrences (all)	50	6	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	21 / 202 (10.40%)	4 / 53 (7.55%)	
occurrences (all)	23	4	
Abdominal pain upper			
subjects affected / exposed	15 / 202 (7.43%)	1 / 53 (1.89%)	
occurrences (all)	18	1	
Constipation			
subjects affected / exposed	34 / 202 (16.83%)	1 / 53 (1.89%)	
occurrences (all)	44	1	
Diarrhoea			
subjects affected / exposed	81 / 202 (40.10%)	2 / 53 (3.77%)	
occurrences (all)	124	2	
Dry mouth			
subjects affected / exposed	12 / 202 (5.94%)	0 / 53 (0.00%)	
occurrences (all)	12	0	
Nausea			
subjects affected / exposed	73 / 202 (36.14%)	4 / 53 (7.55%)	
occurrences (all)	116	6	
Oral pain			
subjects affected / exposed	12 / 202 (5.94%)	1 / 53 (1.89%)	
occurrences (all)	13	1	
Stomatitis			

subjects affected / exposed	139 / 202 (68.81%)	10 / 53 (18.87%)	
occurrences (all)	370	30	
Toothache			
subjects affected / exposed	13 / 202 (6.44%)	2 / 53 (3.77%)	
occurrences (all)	14	2	
Vomiting			
subjects affected / exposed	31 / 202 (15.35%)	7 / 53 (13.21%)	
occurrences (all)	41	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	70 / 202 (34.65%)	7 / 53 (13.21%)	
occurrences (all)	113	7	
Dyspnoea			
subjects affected / exposed	48 / 202 (23.76%)	3 / 53 (5.66%)	
occurrences (all)	64	3	
Epistaxis			
subjects affected / exposed	36 / 202 (17.82%)	1 / 53 (1.89%)	
occurrences (all)	50	2	
Interstitial lung disease			
subjects affected / exposed	15 / 202 (7.43%)	1 / 53 (1.89%)	
occurrences (all)	17	1	
Nasal congestion			
subjects affected / exposed	12 / 202 (5.94%)	0 / 53 (0.00%)	
occurrences (all)	16	0	
Oropharyngeal pain			
subjects affected / exposed	12 / 202 (5.94%)	1 / 53 (1.89%)	
occurrences (all)	16	1	
Pleural effusion			
subjects affected / exposed	14 / 202 (6.93%)	0 / 53 (0.00%)	
occurrences (all)	17	0	
Pneumonitis			
subjects affected / exposed	36 / 202 (17.82%)	2 / 53 (3.77%)	
occurrences (all)	40	2	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	12 / 202 (5.94%)	2 / 53 (3.77%)	
occurrences (all)	12	2	
Dermatitis acneiform			
subjects affected / exposed	4 / 202 (1.98%)	3 / 53 (5.66%)	
occurrences (all)	5	6	
Dry skin			
subjects affected / exposed	24 / 202 (11.88%)	1 / 53 (1.89%)	
occurrences (all)	28	1	
Erythema			
subjects affected / exposed	15 / 202 (7.43%)	0 / 53 (0.00%)	
occurrences (all)	17	0	
Nail disorder			
subjects affected / exposed	12 / 202 (5.94%)	0 / 53 (0.00%)	
occurrences (all)	13	0	
Pruritus			
subjects affected / exposed	35 / 202 (17.33%)	1 / 53 (1.89%)	
occurrences (all)	40	1	
Rash			
subjects affected / exposed	56 / 202 (27.72%)	0 / 53 (0.00%)	
occurrences (all)	84	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	16 / 202 (7.92%)	0 / 53 (0.00%)	
occurrences (all)	19	0	
Insomnia			
subjects affected / exposed	20 / 202 (9.90%)	3 / 53 (5.66%)	
occurrences (all)	22	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	59 / 202 (29.21%)	7 / 53 (13.21%)	
occurrences (all)	92	7	
Back pain			
subjects affected / exposed	30 / 202 (14.85%)	3 / 53 (5.66%)	
occurrences (all)	34	4	
Bone pain			

subjects affected / exposed	13 / 202 (6.44%)	1 / 53 (1.89%)	
occurrences (all)	15	1	
Myalgia			
subjects affected / exposed	16 / 202 (7.92%)	4 / 53 (7.55%)	
occurrences (all)	18	4	
Pain in extremity			
subjects affected / exposed	27 / 202 (13.37%)	2 / 53 (3.77%)	
occurrences (all)	36	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 202 (5.94%)	4 / 53 (7.55%)	
occurrences (all)	13	4	
Conjunctivitis			
subjects affected / exposed	12 / 202 (5.94%)	1 / 53 (1.89%)	
occurrences (all)	16	1	
Gastroenteritis			
subjects affected / exposed	11 / 202 (5.45%)	1 / 53 (1.89%)	
occurrences (all)	11	3	
Nasopharyngitis			
subjects affected / exposed	29 / 202 (14.36%)	6 / 53 (11.32%)	
occurrences (all)	53	15	
Pneumonia			
subjects affected / exposed	27 / 202 (13.37%)	2 / 53 (3.77%)	
occurrences (all)	27	2	
Sinusitis			
subjects affected / exposed	14 / 202 (6.93%)	1 / 53 (1.89%)	
occurrences (all)	17	1	
Upper respiratory tract infection			
subjects affected / exposed	33 / 202 (16.34%)	4 / 53 (7.55%)	
occurrences (all)	46	9	
Urinary tract infection			
subjects affected / exposed	31 / 202 (15.35%)	6 / 53 (11.32%)	
occurrences (all)	43	6	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	64 / 202 (31.68%)	5 / 53 (9.43%)	
occurrences (all)	74	7	
Hypercalcaemia			
subjects affected / exposed	1 / 202 (0.50%)	3 / 53 (5.66%)	
occurrences (all)	2	3	
Hypercholesterolaemia			
subjects affected / exposed	54 / 202 (26.73%)	7 / 53 (13.21%)	
occurrences (all)	71	6	
Hypertriglyceridaemia			
subjects affected / exposed	72 / 202 (35.64%)	5 / 53 (9.43%)	
occurrences (all)	118	5	
Hyperglycaemia			
subjects affected / exposed	59 / 202 (29.21%)	7 / 53 (13.21%)	
occurrences (all)	92	12	
Hyperlipidaemia			
subjects affected / exposed	17 / 202 (8.42%)	0 / 53 (0.00%)	
occurrences (all)	18	0	
Hypophosphataemia			
subjects affected / exposed	14 / 202 (6.93%)	1 / 53 (1.89%)	
occurrences (all)	27	1	
Hypokalaemia			
subjects affected / exposed	32 / 202 (15.84%)	2 / 53 (3.77%)	
occurrences (all)	53	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2012	The purpose of the amendment was to correct the dosage strength of the oral dexamethasone mouth rinse to be administered in the stomatitis therapeutic intervention; to add that patients who discontinued study treatment for any reason other than disease progression or consent withdrawal continued to have tumor assessments until disease progression or until new anticancer therapy was initiated; to add that the ratio for randomization in the stomatitis therapeutic intervention was 1:1 and to remove progesterone receptor from the population description. No patient was enrolled into the study until this amendment
28 May 2013	The main purpose of the amendment was to clarify that the dexamethasone therapeutic investigation was only conducted in countries where an alcohol-free 0.5 mg/5 ml dexamethasone solution was commercially available. The availability of alcohol-free dexamethasone solution at the dosage specified in the protocol was geographically limited and this clarification allowed all countries to participate in the study to investigate the activity of everolimus in combination with letrozole in first line and in combination with exemestane in second line even though they cannot participate in the stomatitis assessment part.
17 March 2014	The main purpose of the amendment was to describe the process for implementing a centralized key eligibility check prior to enrollment of patients to the study. The management of data from OSDQs was also been clarified since the data from the questionnaires were not being entered in a separate electronic database by a designated CRO. Indeed, the data from the OSDQ were entered in the study database by the investigational staff. In addition, the calculation of the clinical benefit rate was clarified to mention that patients with non-measurable disease only at Baseline were included into the numerator of CBR, if they achieved a complete response or stable disease lasting 24 weeks or longer. The wording used to describe the censoring rule for PFS was also clarified. These changes were only to add clarity and did not impact the statistical analysis
10 August 2015	The main purpose of the amendment was to clarify that patients who were benefiting from treatment with everolimus at the time of overall survival analysis could discontinue this study and transition to commercial everolimus or to a rollover study. The study closure would occur once the last patient last visit in the study had been documented. In addition, the amendment clarified the timing of the analysis of PFS for second-line treatment. This analysis will be performed 18 months after last patient first visit (LPFV) only if there is an adequate number of patients in second-line treatment at that time. Otherwise, the analysis will be performed 24 months after LPFV at the same time as the overall survival analysis.

14 February 2017	The main purpose of the amendment was to add an Extension Phase for up to three years to continue to monitor safety and provide access to treatment for patients who are continuing to benefit from treatment with everolimus following the overall survival cutoff which is 24 months post last patient first visit (LPFV) of the core study phase. The first line combination treatment (everolimus + letrozole) is not approved in label for any country and for the second line combination (everolimus + exemestane) some countries mandate that the treatment be provided without cost to patients and some countries have limited availability of supply. For these reasons, treatment was continued to be provided to patients receiving treatment at the time of implementation of this amendment. Treatment was provided for the respective line of treatment (first or second) that the patients are currently receiving at the time of starting the Extension Phase. During the Extension Phase, patients were evaluated as per institution's standard of care to determine clinical benefit and safety was monitored as per the protocol requirements. The purpose of the extension was to continue safety monitoring and provide access to treatment; the only efficacy assessment to be collected was the physician's determination of whether or not the patient was continuing to clinically benefit from the study treatment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: