Sponsor

Novartis Pharma GmbH, Nuremberg, Germany

Generic Drug Name

Everolimus

Exemestane

Trial Indication(s)

Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer

Protocol Number

CRAD001JDE49

Protocol Title

A Phase IIIB, Multi-Center, Open Label Study For Postmenopausal Women With Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Treated With Everolimus (RAD001) in Combination With Exemestane: 4EVER Efficacy, Safety, Health Economics, Translational Research

Clinical Trial Phase

Phase IIIB

Phase of Drug Development

IIIB

Study Start/End Dates

Study start: 25 Jun 2012 (first patient first visit) to 26 Nov 2013 (last patient last visit)

Reason for Termination (If applicable)

N.A.

Study Design/Methodology

This was a national, multi-center, open-label, single-arm, phase IIIB study, designed to evaluate the overall response rate (ORR) after 24 weeks of treatment with a combination of everolimus (10 mg daily) and exemestane (25 mg daily) in postmenopausal women with hormone receptor (HR) positive locally advanced or metastatic breast cancer progressing following prior therapy with non-steroidal aromatase inhibitors (NSAIs).

Centers

86 centers in Germany

Publication

N.A.

Objectives:

Primary objective

To assess the overall response rate (ORR) in postmenopausal women with hormone receptor (HR) positive breast cancer progressing following prior therapy with NSAIs treated with the combination of everolimus and exemestane.

Secondary objectives

To evaluate the following:

- ORR after 48 weeks of treatment.
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety
- Change in health-related quality of life (HRQoL) scores over time
- Health resource utilization

  The objective health resource utilization had to be cancelled due to difficulties in obtaining an adequate reference dataset.

Test Product (s), Dose(s), and Mode(s) of Administration

A daily dose of oral tablets of everolimus 10 mg and a daily dose of oral tablets of exemestane 25 mg.

Statistical Methods

Analysis sets:

- The FAS1 consisted of all patients to whom treatment was assigned and who received at least 1 dose of study drug with the exception of patients from site 184 and 187 due to an issue of GCP non-compliance.

- The FAS2 consisted of all patients to whom treatment was assigned and who received at least 1 dose of study drug.
- The PPS consisted of a subset of patients of the FAS1 who did not show major protocol deviations.
- The safety set consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Efficacy:

The primary endpoint ORR after 24 weeks of treatment was analyzed along with the disease control rate (DCR) and the individual categories of best overall response using frequency tables and associated two-sided exact 95% confidence intervals (CIs) (Clopper-Pearson method). The primary analysis was performed with the FAS1. As supportive analysis, the primary analysis was repeated for the FAS2 and PPS. As subgroup analysis, the primary analysis was repeated for patients with *vs*. without prior therapy with exemestane and for patients with *vs*. without prior chemotherapy in metastatic setting. The secondary endpoint ORR after 48 weeks of treatment was analyzed analogously to the primary analysis.

The secondary endpoints PFS and OS were analyzed using the Kaplan-Meier method. Percentiles (25%, median, 75%) of the event time distribution were presented along with their two-sided 95% CIs. Subgroup analyses were performed as for the ORR. An additional subgroup analysis of PFS was performed for patients entering the study at early therapy lines (1st to 4th line) *vs*. patients at later therapy lines (≥ 5th line).

HRQoL: HRQoL measures were analyzed descriptively. To account for a high number of missing values, the EORTC QLQ-C30 global health status/QoL score and the EQ VAS score were in addition analyzed using a mixed model for repeated measures (MMRM). Time to > 5% deterioration in EORTC QLQ-C30 global health status/QoL score was analyzed using the Kaplan-Meier method.

Safety: Incidences of AEs, SAEs and other significant AEs were analyzed descriptively. Detailed analyses included presentation by CTCAE severity grade and of (S)AEs with a suspected relationship the study drugs (based in investigator's assessment). Other safety data were analyzed descriptively.

Bioanalytics - biomarkers for bone turnover: Bone turnover biomarkers were analyzed descriptively in relation to the patient's overall lesion response.

Due to the exploratory nature of the trial, no adjustment for multiplicity was foreseen nor performed. No interim analysis was planned or performed.

Study Population: Key Inclusion/Exclusion Criteria

Main Inclusion criteria:

- Metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy or any other non-systemic treatment.
- Histological or cytological confirmation of estrogen receptor positive (ER+) and/or progesterone receptor positive (PgR+), human epidermal growth factor receptor 2 (HER2) negative breast cancer Postmenopausal women. Disease progression following prior therapy with non steroidal aromatase inhibitors (NSAI), defined as: Recurrence while on, or following completion of an adjuvant treatment with Letrozole or Anastrozole, or Progression while on or following completion of Letrozole or Anastrozole treatment for ABC/MBC.
- Radiological evidence of recurrence or progression on last systemic therapy prior to enrollment.
- Patients must have at least one lesion that can be accurately measured or bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease.
- Written informed consent obtained before any screening procedure and according to local guidelines.
- Other protocol defined inclusion criteria apply.

Main Exclusion criteria:

- HER2-overexpressing patients by local laboratory testing (IHC 3+ staining or in situ hybridization positive).
- Patients with only non-measurable lesions other than bone metastasis (e.g. pleural effusion, ascites etc.).
- Previous treatment with mTOR inhibitors or known hypersensitivity to mTOR inhibitors.
- Symptomatic brain or other CNS metastases. Previously treated brain metastases are allowed provided the patient is free of symptoms, prior radiotherapy for brain metastasis was more than four weeks before enrollment and the dose of corticosteroids is low (i.e. ≤ 10 mg/d Prednisolone equivalent) and stable for at least two weeks prior to enrollment.
- Patients with Hepatitis B or C or with a history of Hepatitis B or C. Patients unwilling to or unable to comply with the protocol. Other protocol defined exclusion criteria apply.

Participant Flow Table

Patient disposition (all patients)

	everolimus + exemestane n (%)
Screened	330
Enrolled/treated (everolimus + exemestane)	299 (100.0)
Continued study treatment (everolimus) for 48 weeks	36 (12.0)
Discontinued study treatment (everolimus) earlier	255 (85.3)
Missing data on treatment continuation	8 (2.7)
Primary reason for discontinuation	
Disease progression	116 (38.8)
Adverse event(s)	74 (24.7)
Death	24 (8.0)
Subject withdrew consent	19 (6.4)
Protocol deviation	6 (2.0)
Administrative problems	6 (2.0)
New cancer therapy	5 (1.7)
Abnormal laboratory value(s)	3 (1.0)
Lost to follow-up	2 (0.7)
Abnormal test procedure result(s)	0 (0.0)

Note: The information provided in this table is driven from the End of Treatment CRF. Therefore, information about AEs leading to discontinuation of study treatment may be slightly different from the information retrieved from the Adverse Events CRF.

Baseline Characteristics

Demographic summary (safety set)

		everolimus + exemestane N=299
Age [years]	Mean ± SD	65.4 ± 9.3
	Median [Range]	67.0 [35 – 87]
	Missing	0
Age group – n (%)	< 65 years	134 (44.8)
	≥ 65 years	165 (55.2)
	Missing	0
Race – n (%)	Caucasian	296 (99.3)
	Black	0 (0.0)
	Asian	2 (0.7)
	Other	0 (0.0)
	Missing	1
Weight [kg] [1]	Mean ± SD	69.4 ± 13.4
	Median [Range]	67.4 [40 – 111]
	Missing	51
ECOG performance status [1, 2] – n (%)	0	168 (58.5)
	1	108 (37.6)
	2	10 (3.5)
	3	1 (0.3)
	Missing	11

SD = standard deviation, ECOG = Eastern Cooperative Oncology Group.
[1] At baseline.
[2] No patient had an ECOG performance status of 4.

Summary of Efficacy

Primary efficacy results

Primary Outcome Result(s)

ORR after 24 weeks of treatment – primary analysis (FAS1)

	everolimus + exemestane N = 281	
	n (%)	95% CI [1]
Overall response rate (ORR) [2]	25 (8.9)	[5.8 – 12.9]
Disease control rate (DCR) [3]	94 (33.5)	[28.0 – 39.3]
Best overall response [4]		
Complete response (CR)	1 (0.4)	
Partial response (PR)	24 (8.5)	
Stable disease (SD)	69 (24.6)	
Progressive disease (PD)	105 (37.4)	
Unknown	82 (29.2)	

CI = confidence interval.
[1] Clopper-Pearson CI
[2] Proportion of patients with best overall response CR or PR; primary endpoint
[3] Proportion of patients with best overall response CR or PR or SD
[4] Based on local assessment, without required confirmation of response by repeated assessment

ORR after 24 weeks of treatment – supportive analyses (FAS2, PPS)

	everolimus + exemestane	
	n (%)	95% CI [1]
FAS2	*N = 299*	
Overall response rate (ORR) [2]	25 (8.4)	[5.5 – 12.1]
Disease control rate (DCR) [3]	96 (32.1)	[26.8 – 37.7]
Best overall response [4]		
Complete response (CR)	1 (0.3)	
Partial response (PR)	24 (8.0)	
Stable disease (SD)	71 (23.7)	
Progressive disease (PD)	112 (37.5)	
Unknown	91 (30.4)	
PPS	*N = 162*	
Overall response rate (ORR) [2]	15 (9.3)	[5.3 – 14.8]
Disease control rate (DCR) [3]	49 (30.2)	[23.3 – 37.9]
Best overall response [4]		
Complete response (CR)	1 (0.6)	
Partial response (PR)	14 (8.6)	
Stable disease (SD)	34 (21.0)	
Progressive disease (PD)	70 (43.2)	
Unknown	43 (26.5)	

CI = confidence interval.
[1] Clopper-Pearson CI
[2] Proportion of patients with best overall response CR or PR
[3] Proportion of patients with best overall response CR or PR or SD
[4] Based on local assessment, without required confirmation of response by repeated assessment

ORR after 24 weeks of treatment – subgroup analyses (FAS1)

	Prior therapy with exemestane		Prior chemotherapy in metastatic setting	
	No	Yes	No	Yes
	N = 190	N = 91	N = 130	N = 151
Overall response rate (ORR) [1]				
n (%)	17 (8.9)	8 (8.8)	15 (11.5)	10 (6.6)
95% CI [2]	[5.3 – 13.9]	[3.9 – 16.6]	[6.6 – 18.3]	[3.2 – 11.8]
Disease control rate (DCR) [3]				
n (%)	64 (33.7)	30 (33.0)	55 (42.3)	39 (25.8)
95% CI [2]	[27.0 – 40.9]	[23.5 – 43.6]	[33.7 – 51.3]	[19.1 – 33.6]
Best overall response [4] – n (%)				
Complete response (CR)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.7)
Partial response (PR)	16 (8.4)	8 (8.8)	15 (11.5)	9 (6.0)
Stable disease (SD)	47 (24.7)	22 (24.2)	40 (30.8)	29 (19.2)
Progressive disease (PD)	72 (37.9)	33 (36.3)	41 (31.5)	64 (42.4)
Unknown	54 (28.4)	28 (30.8)	34 (26.2)	48 (31.8)

CI = confidence interval.

[1] Proportion of patients with best overall response CR or PR

[2] Clopper-Pearson CI

[3] Proportion of patients with best overall response CR or PR or SD

[4] Based on local assessment, without required confirmation of response by repeated assessment

Note: The number of patients in the subgroup "prior therapy with exemestane" differs from the subgroup shown under baseline characteristics. The subgroup under baseline characteristics includes all patients with exemestane documented on the Prior Antineoplastic Therapy – Medications CRF. The subgroup shown here includes the same patients plus all patients who had received exemestane > 1 day before the everolimus therapy start, i.e., who were already on exemestane monotherapy when they started everolimus, as documented on the Dosage Administration Record CRF.

Secondary Outcome Result(s)

ORR after 48 weeks of treatment (FAS1)

	everolimus + exemestane N = 281	
	n (%)	95% CI [1]
Overall response rate (ORR) [2]	29 (10.3)	[7.0 – 14.5]
Disease control rate (DCR) [3]	101 (35.9)	[30.3 – 41.9]
Best overall response [4]		
Complete response (CR)	1 (0.4)	
Partial response (PR)	28 (10.0)	
Stable disease (SD)	72 (25.6)	
Progressive disease (PD)	112 (39.9)	
Unknown	68 (24.2)	

CI = confidence interval.
[1] Clopper-Pearson CI
[2] Proportion of patients with best overall response CR or PR
[3] Proportion of patients with best overall response CR or PR or SD
[4] Based on local assessment, without required confirmation of response by repeated assessment

ORR after 48 weeks of treatment – subgroup analyses (FAS1)

	Prior therapy with exemestane		Prior chemotherapy in metastatic setting	
	No	Yes	No	Yes
	N = 190	N = 91	N = 130	N = 151
Overall response rate (ORR) [1]				
n (%)	21 (11.1)	8 (8.8)	17 (13.1)	12 (7.9)
95% CI [2]	[7.0 – 16.4]	[3.9 – 16.6]	[7.8 – 20.1]	[4.2 – 13.5]
Disease control rate (DCR) [3]				
n (%)	68 (35.8)	33 (36.3)	57 (43.8)	44 (29.1)
95% CI [2]	[29.0 – 43.0]	[26.4 – 47.0]	[35.2 – 52.8]	[22.0 – 37.1]
Best overall response [4] – n (%)				
Complete response (CR)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.7)
Partial response (PR)	20 (10.5)	8 (8.8)	17 (13.1)	11 (7.3)
Stable disease (SD)	47 (24.7)	25 (27.5)	40 (30.8)	32 (21.2)
Progressive disease (PD)	77 (40.5)	35 (38.5)	44 (33.8)	68 (45.0)
Unknown	45 (23.7)	23 (25.3)	29 (22.3)	39 (25.8)

CI = confidence interval.

[1] Proportion of patients with best overall response CR or PR

[2] Clopper-Pearson CI

[3] Proportion of patients with best overall response CR or PR or SD

[4] Based on local assessment, without required confirmation of response by repeated assessment

Note: The number of patients in the subgroup "prior therapy with exemestane" differs from the respective subgroup shown under baseline characteristics.

Kaplan-Meier estimates of PFS and OS (FAS1)

		everolimus + exemestane N = 281
Progression-free survival (PFS)		
Patients with event (raw data) – n (%)		168 (59.8)
Patients censored (raw data) – n (%)		113 (40.2)
PFS time [months] [1]	25% percentile	3.1 [2.9 – 3.7]
	Median	5.6 [5.4 – 6.0]
	75% percentile	10.7 [8.5 – 11.1]
PFS rate at … [%] [2]	24 weeks	50.0
	48 weeks	19.3
Overall survival (OS)		
Patients with event (raw data) – n (%)		101 (35.9)
Patients censored (raw data) – n (%)		180 (64.1)
OS time [months] [1, 3]	25% percentile	7.8 [5.4 – 9.8]
	Median	-
	75% percentile	-
OS rate at … [%] [2]	24 weeks	79.4
	48 weeks	66.9

CI = confidence interval.
Progression based on local assessment
[1] Kaplan-Meier estimates [95% CI] of PFS/OS time [months]
[2] Kaplan-Meier estimates of proportion [%] of patients surviving without progression (PFS)/surviving (OS) until week 24/48
[3] Some values are not calculable due to the fortunately low number of events compared to the number of censored data.

Kaplan-Meier estimates of PFS and OS – subgroup analyses (FAS1)

	Prior therapy with exemestane		Prior chemotherapy in metastatic setting	
	No	Yes	No	Yes
	N = 190	N = 91	N = 130	N = 151
Progression-free survival (PFS)				
Patients with event/censored (raw data) – n (%)				
With event	112 (58.9)	56 (61.5)	73 (56.2)	95 (62.9)
Censored	78 (41.1)	35 (38.5)	57 (43.8)	56 (37.1)
PFS time [months] [1]				
25% percentile	3.1 [2.9 – 4.0]	3.2 [2.8 – 3.9]	4.6 [3.1 – 5.4]	2.9 [2.7 – 3.3]
Median	5.5 [5.3 – 6.3]	5.6 [4.2 – 6.9]	6.2 [5.6 – 7.7]	5.2 [4.2 – 5.5]
75% percentile	10.8 [8.2 – 11.1]	9.1 [7.6 – 11.2]	11.1 [8.4 – 11.6]	9.1 [7.8 – 11.0]
PFS rate at … [%] [2]				
24 weeks	49.6	50.7	62.6	38.3
48 weeks	20.2	17.2	25.8	14.0
Overall survival (OS)				
Patients with event/censored (raw data) – n (%)				
With event	72 (37.9)	29 (31.9)	29 (22.3)	72 (47.7)
Censored	118 (62.1)	62 (68.1)	101 (77.7)	79 (52.3)
OS time [months] [1, 3]				
25% percentile	7.3 [5.2 – 9.9]	8.0 [4.1 – 12.8]	15.4 [8.2 –]	5.3 [4.0 – 7.3]
Median	- [14.8 –]	-	-	12.8 [9.9 –]
75% percentile	-	-	-	-
OS rate at … [%] [2]				
24 weeks	78.3	81.8	87.1	72.8
48 weeks	66.3	68.2	80.3	55.3

CI = confidence interval.
Progression based on local assessment.

[1] Kaplan-Meier estimates [95% CI] of PFS/OS time [months]
[2] Kaplan-Meier estimates of proportion [%] of patients surviving without progression (PFS)/surviving (OS) until week 24/48
[3] Some values are not calculable due to the fortunately low number of events compared to the number of censored data.

Note: The number of patients in the subgroup "prior therapy with exemestane" differs from the respective subgroup shown under baseline characteristics.

Kaplan-Meier estimates of PFS – subgroup analysis by therapy line (FAS1)

	1st to 4th therapy line	5th therapy line and later
	N = 190	N = 87
Progression-free survival (PFS)		
Patients with event/censored (raw data) – n (%)		
With event	105 (55.3)	61 (70.1)
Censored	85 (44.7)	26 (29.9)
PFS time [months] [1]		
25% percentile	3.7 [3.0 – 4.9]	2.9 [2.4 – 3.0]
Median	5.7 [5.5 – 6.7]	4.8 [3.3 – 5.5]
75% percentile	10.9 [10.6 – 11.3]	8.5 [6.0 – 9.3]
PFS rate at … [%] [2]		
24 weeks	56.6	37.6
48 weeks	24.9	8.8

CI = confidence interval.
Progression based on local assessment.
[1] Kaplan-Meier estimates [95% CI] of PFS time [months]

[2] Kaplan-Meier estimates of proportion [%] of patients surviving without until week 24/48

Change in EORTC QLQ-C30 (subscale) scores over time (FAS1)

Secondary Outcome results?		Score Baseline N = 280	Score difference to baseline Week 12 N = 190	Week 24 N = 113	Week 36 N = 61	EOT N = 176	Score EOT N = 176
Global health status/QoL	Sample values						
	n [1]	253	147	86	50	100	100
	M	54.6	-6.2	-4.2	-3.2	-8.8	48.2
	SD	21.8	20.8	24.0	20.3	18.8	20.9
	Modelled values [2]						
	M	54.7	-5.1***	-3.5+	-1.6	-5.5+	49.1
	SE	1.3	1.5	2.0	2.7	3.3	
Physical functioning	M	66.6	-6.6	-6.9	-5.4	-6.2	64.1
	SD	24.6	17.3	16.9	17.6	19.6	25.4
Role functioning	M	55.9	-7.9	-7.7	-2.4	-6.7	52.4
	SD	35.4	28.5	32.0	25.7	28.4	31.2
Emotional functioning	M	62.7	-4.9	0.2	-0.4	-3.5	58.5
	SD	24.3	23.2	24.4	19.1	23.5	24.3
Cognitive functioning	M	79.6	-3.6	-4.7	-4.9	-4.2	72.3
	SD	24.4	22.9	25.5	22.8	24.8	24.4
Social functioning	M	66.9	-5.8	-7.3	-5.1	-11.5	58.6
	SD	30.2	31.7	29.4	30.6	29.6	30.2
Fatigue	M	47.4	13.1	12.5	7.2	10.9	54.7
	SD	29.1	26.5	31.3	26.2	31.2	27.9
Nausea and vomiting	M	11.0	7.4	4.3	3.1	5.3	14.8
	SD	19.8	25.1	20.8	17.8	26.0	24.9
Pain	M	43.6	2.8	6.2	2.7	1.0	43.1
	SD	31.7	28.6	28.4	23.4	28.8	31.4
Dyspnoea	M	34.8	13.5	8.6	3.5	7.9	44.3
	SD	33.2	29.5	31.4	29.7	28.8	33.4
Insomnia	M	43.8	6.2	8.4	3.5	11.2	50.5

Secondary Outcome results?		Score Baseline N = 280	Score difference to baseline Week 12 N = 190	Week 24 N = 113	Week 36 N = 61	EOT N = 176	Score EOT N = 176
	SD	34.4	34.2	36.7	33.9	32.4	32.3
Appetite loss	M	28.2	24.3	16.3	15.3	16.2	40.4
	SD	33.6	45.4	44.2	44.0	37.0	36.8
Constipation	M	14.6	-3.1	-5.4	-6.3	-1.0	14.8
	SD	26.5	27.2	26.5	32.0	26.6	28.9
Diarrhea	M	12.6	13.0	13.2	8.2	10.7	20.0
	SD	23.3	35.3	28.6	24.1	28.8	30.0
Financial difficulties	M	16.5	3.2	1.6	3.5	4.8	24.5
	SD	27.3	23.2	22.4	20.9	21.5	32.6

EOT = end of treatment, QoL = quality of life, M = mean, SD = standard deviation, SE = standard error, n = number of observations. N corresponds to the number of patients of the FAS1 (N = 281) who performed the respective visit.

[1] The number of observations n was similar for all other scores as missing values occurred mostly due to missing questionnaires.

[2] Estimated by MMRM (mixed model for repeated measures) with time as fixed effect and patient as random effect; *** $p < 0.001$ $^{+}$ $p < 0.1$.

Change in EORTC QLQ-BR23 (subscale) scores over time (FAS1)

		Score	Score change from baseline				Score
		Baseline	Week 12	Week 24	Week 36	EOT	EOT
		N = 280	N = 190	N = 113	N = 61	N = 176	N = 176
Functioning: body image	n [1]	251	146	84	48	98	108
	M	74.9	-2.5	-1.9	0.6	-1.0	74.1
	SD	27.1	20.6	23.0	24.0	23.7	26.7
Functioning: sexual functioning	M	16.4	-2.8	-2.6	-0.9	-2.0	13.3
	SD	24.4	21.1	20.4	22.6	21.4	19.9
Functioning: sexual enjoyment [2]	M	62.6	-8.3	-27.8	-16.7	-19.4	48.1
	SD	26.0	22.8	27.8	18.3	30.0	30.7
Functioning: future perspective	M	34.8	-1.4	5.2	7.8	3.7	38.5
	SD	30.4	32.8	32.1	23.3	33.1	32.4
Arm symptoms	M	27.1	1.0	0.7	4.3	2.3	30.5
	SD	29.0	23.0	21.0	28.4	26.0	25.2
Breast symptoms	M	11.4	2.6	2.6	-3.0	0.9	13.0
	SD	17.1	18.7	16.0	15.3	13.2	16.3
Systemic therapy side effects	M	25.8	11.4	8.6	9.1	8.4	32.0
	SD	17.4	18.1	21.1	17.8	19.3	18.7
Upset by hair loss	M	10.6	5.5	5.5	-1.6	0.8	12.1
	SD	24.2	25.1	30.9	34.9	29.8	25.8

EOT = end of treatment, M = mean, SD = standard deviation, n = number of observations. N corresponds to the number of patients of the FAS1 (N = 281) who performed the respective visit.

EORTC QLQ-BR23 scales range from 0 to 100. High scores for functional scales (body image to sexual enjoyment) represent high level of functioning. High scores for symptom scales (arm symptoms to upset by hair loss) represent high levels of symptomatology.

[1] The number of observation n was similar for other subscale scores as missing values occurred mostly due to missing questionnaires. An exception is [2] with > 80% missing values at all visits.

Time to > 5% deterioration in EORTC QLQ-C30 global health status/QoL score (FAS1)

		everolimus + exemestane N = 210
Progression-free survival (PFS)		
Patients with event (raw data) – n (%)		123 (58.6)
Patients censored (raw data) – n (%)		87 (41.4)
5% deterioration time [months] [1]	25% percentile	2.8 [2.8 – 2.8]
	Median	4.2 [3.0 – 5.5]
	75% percentile	11.0 [7.1 –]
Rate of patients without deterioration at … [%] [2]	24 weeks	41.8
	48 weeks	24.6

CI = confidence interval. N corresponds to the number of patients of the FAS1 (N = 281) with baseline assessment and at least 1 post-baseline visit.

[1] Kaplan-Meier estimates [95% CI] of time to deterioration [months]. The CI upper boundary of the 75% percentile is not calculable.

[2] Kaplan-Meier estimates of proportion [%] of patients without deterioration until week 24/48

Change in EQ VAS score over time (FAS1)

		Score	Score change from baseline				Score
		Baseline	Week 12	Week 24	Week 36	EOT	EOT
EQ VAS score		N = 280	N = 190	N = 113	N = 61	N = 176	N = 176
Sample values	n	243	138	81	44	96	111
	M	60.8	-2.9	-5.1	-4.8	-5.3	56.0
	SD	21.2	19.5	23.4	24.3	20.9	20.6
Modelled values [1]	M	60.4	-3.5*	-4.5*	-0.3	-2.3	58.1
	SE	1.3	1.4	1.9	2.5	3.1	

EOT = end of treatment, VAS = visual analogue scale, M = mean, SD = standard deviation, SE = standard error, n = number of observations. N corresponds to the number of patients of the FAS1 (N = 281) who performed the respective visit.

[1] Estimated by MMRM (mixed model for repeated measures) with time as fixed effect and patient as random effect; * $p < 0.05$.

The EQ VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable heath state).

Change in EQ-5D 5L health state dimensions over time (FAS1)

	Baseline	EOT	Change [1] baseline to EOT	
	N = 280	N = 176	N = 176	
Mobility – n (%)				
No problems in walking about	96 (37.2)	41 (36.6)	I	14 (13.6)
Slight problems in walking about	69 (26.7)	27 (24.1)	NC	61 (59.2)
Moderate problems in walking about	55 (21.3)	21 (18.8)	D	28 (27.3)
Severe problems in walking about	37 (14.3)	22 (19.6)	M	73
Unable to walk about	1 (0.4)	1 (0.9)		
Missing	22	64		
Self-care – n (%)				
No problems washing or dressing oneself	207 (80.2)	84 (75.0)	I	5 (4.8)
Slight problems washing or dressing os.	28 (10.9)	11 (9.8)	NC	85 (82.5)
Moderate problems washing or dressing os.	15 (5.8)	14 (12.5)	D	13 (12.6)
Severe problems washing or dressing os.	6 (2.3)	3 (2.7)	M	73
Unable to wash or dress os.	2 (0.8)	0 (0.0)		
Missing	22	64		
Usual activities – n (%)				
No problems doing usual activities	100 (39.1)	38 (33.6)	I	13 (12.7)
Slight problems doing usual activities	73 (28.5)	33 (29.2)	NC	64 (62.1)
Moderate problems doing usual activities	53 (20.7)	28 (24.8)	D	26 (25.3)
Severe problems doing usual activities	29 (11.3)	12 (10.6)	M	73
Unable to do usual activities	1 (0.4)	2 (1.8)		
Missing	24	63		
Pain/discomfort – n (%)				
No pain or discomfort	51 (19.8)	15 (13.3)	I	17 (16.4)
Slight pain or discomfort	98 (38.0)	37 (32.7)	NC	53 (51.0)
Moderate pain or discomfort	75 (29.1)	43 (38.1)	D	34 (32.7)

Severe pain or discomfort	30 (11.6)	15 (13.3)	M	72
Extreme pain or discomfort	4 (1.6)	3 (2.7)		
Missing	22	63		
Anxiety/depression – n (%)				
Not anxious or depressed	104 (40.6)	25 (22.1)	I	13 (12.8)
Slightly anxious or depressed	88 (34.4)	56 (49.6)	NC	56 (54.9)
Moderately anxious or depressed	50 (19.5)	24 (21.2)	D	33 (32.3)
Severely anxious or depressed	12 (4.7)	7 (6.2)	M	74
Extremely anxious or depressed	2 (0.8)	1 (0.9)		
Missing	24	63		

EOT = end of treatment. N corresponds to the number of patients of the FAS1 (N = 281) who performed the respective visit.
[1] Number and % of patients with improvement (I), no change (NC), deterioration (D), or missing value (M).

Prevalence of anxiety and depression according to HADS-D (FAS1)

	Baseline N = 280	Week 12 N = 190	Week 24 N = 113	Week 36 N = 61	EOT N = 176
Anxiety – % [1]					
Within normal range [0 – 7] [2]	62.3	56.3	60.2	63.5	50.4
Suggestive of presence [8 – 10]	23.1	25.6	25.8	25.0	26.5
Probable presence – severe [11 – 14]	11.9	15.6	11.8	11.5	14.2
Probable presence – very severe [15 – 21]	2.7	2.5	2.2	0.0	8.8
n Missing	20	30	20	9	63
Depression – % [1]					
Within normal range [0 – 7]	68.5	54.4	66.7	71.7	58.4
Suggestive of presence [8 – 10]	15.8	23.1	17.2	11.3	23.0
Probable presence – severe [11 – 14]	11.2	16.9	10.8	11.3	11.5
Probable presence – very severe [15 – 21]	4.6	5.6	5.4	5.7	7.1
n Missing	20	30	20	8	63

EOT = end of treatment. N corresponds to the number of patients of the FAS1 (N = 281) who performed the respective visit.
[1] Percentage of patients in respective category
[2] Score range of respective category

Change in HADS-D subscale scores over time (FAS1)

		Score	Score change from baseline				Score
		Baseline	Week 12	Week 24	Week 36	EOT	EOT
		N = 280	N = 190	N = 113	N = 61	N = 176	N = 176
Anxiety	n [1]	260	151	89	49	103	113
	M	6.6	0.2	-0.1	-0.7	0.7	7.6
	SD	3.7	3.2	3.3	3.2	3.3	4.2
Depression	M	6.0	1.4	0.9	0.5	1.2	7.2
	SD	4.1	3.3	3.3	2.5	3.4	4.2

EOT = end of treatment, M = mean, SD = standard deviation, n = number of observations. N corresponds to the number of patients of the FAS1 (N = 281) who performed the respective visit.

HADS-D subscales range from 0 to 21, high scores representing high levels of anxiety/depression.

[1] The number of observation n was similar for the depression scores as missing values occurred mostly due to missing questionnaires.

Summary of Safety

Safety Results

Adverse Events by Preferred Term and CTCAE grade:

Incidence of most common grade 3 – 4 AEs by preferred term and CTCAE maximum severity grade (≥ 2% grade 3 – 4 or ≥ 1% grade 4 AEs) (safety set)

	everolimus + exemestane N = 299			
Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at least 1 AE	**30 (10.0)**	**88 (29.4)**	**137 (45.8)**	**39 (13.0)**
Stomatitis [1]	70 (23.4)	52 (17.4)	24 (8.0)	1 (0.3)
General physical health deterioration	6 (2.0)	10 (3.3)	16 (5.4)	4 (1.3)
Dyspnoea [2]	40 (13.4)	20 (6.7)	11 (3.7)	3 (1.0)
Anaemia [3]	12 (4.0)	28 (9.4)	11 (3.7)	2 (0.7)
Malignant neoplasm progression	-	2 (0.7)	5 (1.7)	6 (2.0)
Pneumonia [4]	3 (1.0)	6 (2.0)	5 (1.7)	5 (1.7)
Fatigue	66 (22.1)	32 (10.7)	9 (3.0)	1 (0.3)
Vomiting	22 (7.4)	11 (3.7)	9 (3.0)	1 (0.3)
Decreased appetite	44 (14.7)	23 (7.7)	9 (3.0)	-
Nausea	47 (15.7)	22 (7.4)	8 (2.7)	1 (0.3)
Pleural effusion	-	9 (3.0)	8 (2.7)	1 (0.3)
Gamma-glutamyltransferase increased	5 (1.7)	6 (2.0)	7 (2.3)	1 (0.3)
Pneumonitis [5]	5 (1.7)	10 (3.3)	6 (2.0)	1 (0.3)
Diarrhoea	42 (14.0)	31 (10.4)	6 (2.0)	-
Aspartate aminotransferase increased	11 (3.7)	10 (3.3)	6 (2.0)	-
Alanine aminotransferase increased	14 (4.7)	6 (2.0)	6 (2.0)	-
Urinary tract infection	2 (0.7)	7 (2.3)	5 (1.7)	1 (0.3)

CTCAE = Common Terminology Criteria for Adverse Events, AE = adverse event.

Only the most common grade 3 – 4 AEs are listed. Cut off: Incidence of grade 3 – 4 AEs ≥ 2% or of grade 4 AEs ≥ 1% for preferred term. Preferred terms are listed in descending frequency of grade 3 plus grade 4 SAEs.

AEs listed under similar preferred terms:

[1] "Aphthous stomatitis" 27 patients (15 [5.0%] grade 1, 10 [3.3%] grade 2, 2 [0.7%] grade 3); "Mouth ulceration" 2 patients (1 [0.3%] grade 1, 1 [0.3%] grade 3); "Tongue ulceration" 1 patient (0.3%) grade 2.

[2] "Dyspnoea exertional" 4 patients (2 [0.7%] grade 1, 1 [0.3%] grade 2, 1 [0.3%] grade 3).

[3] "Anaemia of malignant disease" 2 patients (1 [0.3%] grade 2, 1 [0.3%] grade 3).

[4] "Pneumonia streptococcal" 1 patient (0.3%) grade 3.

[5] "Alveolitis" 5 patients (3 [1.0%] grade 1, 1 [0.3%] grade 2, 1 [0.3%] grade 4); "Interstitial lung disease" 3 patients (2 [0.7%] grade 1, 1 [0.3%] grade 2).

Serious Adverse Events and Deaths:

Number of patients who died or experienced other serious or clinically significant AEs (safety set)

Type of event	everolimus + exemestane N = 299 n (%)
Death [1]	36 (12.0)
SAE [2]	142 (47.5)
Discontinued due to AE	77 (25.8)
Discontinued due to SAE	29 (9.7)
Dose adjustment/interruption due to AE	133 (44.5)
Dose adjustment/interruption due to SAE	37 (12.4)

[1] Number of deaths that occurred during the study, during the safety follow-up, or later as a result of a treatment-emergent SAE.

[2] Including fatal SAEs.

Notes:

The number of deaths reported here (36 patients in the safety set) is larger than the number of early study treatment discontinuations due to death (24 patients in the safety set), which includes only deaths that occurred during the treatment phase of the study (not during the safety follow-up), and smaller than the number of death considered for the calculation of OS (101 patients in the FAS1), which includes also deaths that occurred after the safety follow-up during the progression and survival follow-up.

The information provided in this table is driven from the Adverse Events CRF. Therefore, information about (S)AEs leading to discontinuation of study treatment is slightly different from the information retrieved from the End of Treatment CRF.

Fatal SAEs by primary SOC and Preferred Term:

Incidence of fatal SAEs by primary SOC and preferred term (≥ 2 patients) (safety set)

Primary SOC Preferred term	everolimus + exemestane N = 299 n (%)
Patients who died	**36 (12.0%)**
Cardiac disorders	**4 (1.3%)**
Cardiac failure	2 (0.7%)
Gastrointestinal disorders	**2 (0.7%)**
General disorders & administration site conditions	**9 (3.0%)**
General physical health deterioration	5 (1.7%)
Death	2 (0.7%)
Multi-organ failure	2 (0.7%)
Hepatobiliary disorders	**5 (1.7%)**
Hepatic failure	4 (1.3%)
Hepatorenal syndrome	2 (0.7%)
Infections & infestations	**2 (0.7%)**
Pneumonia	2 (0.7%)
Investigations	**1 (0.3%)**
Metabolism & nutrition disorders	**2 (0.7%)**
Neoplasms benign, malignant & unspecified (incl. cysts & polyps)	**15 (5.0%)**
Malignant neoplasm progression	13 (4.3%)
Breast cancer metastatic	2 (0.7%)
Metastases to liver	2 (0.7%)
Metastases to lung	2 (0.7%)
Nervous system disorders	**1 (0.3%)**
Renal & urinary disorders	**4 (1.3%)**

	everolimus + exemestane
Primary SOC	N = 299
Preferred term	n (%)
Renal failure [1]	3 (1.0%)
Respiratory, thoracic & mediastinal disorders	**7 (2.3%)**
Dyspnoea [2]	2 (0.7%)
Vascular disorders	**2 (0.7%)**

SOC = system organ class, SAE = serious adverse event.

On preferred term level, only fatal SAEs occurring in ≥ 2 patients are listed.

Fatal SAEs listed under similar preferred terms:

[1] "Renal failure acute" 1 patient (0.3%).

[2] "Dyspnoea exertional" 1 patient (0.3%).

Note: The number of patients who died reported here (36 patients in the safety set) is larger than the number of early study treatment discontinuations due to death (24 patients in the safety set), which includes only deaths that occurred during the treatment phase of the study (not during the safety follow-up), and smaller than the number of death considered for the calculation of OS (101 patients in the FAS1), which includes also deaths that occurred after the safety follow-up during the progression and survival follow-up.

Serious Adverse Events by Preferred Term and CTCAE grade:

Incidence of most common grade 3 – 4 SAEs by preferred term and CTCAE maximum severity grade (≥ 1% grade 3 – 4 SAEs) (safety set)

	everolimus + exemestane N = 299			
Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at least 1 SAE	**4 (1.3)**	**20 (6.7)**	**71 (23.7)**	**39 (13.0)**
General physical health deterioration	-	5 (1.7)	12 (4.0)	4 (1.3)
Malignant neoplasm progression	-	1 (0.3)	5 (1.7)	6 (2.0)
Pneumonia [1]	2 (0.7)	5 (1.7)	5 (1.7)	5 (1.7)
Pleural effusion	-	3 (1.0)	8 (2.7)	1 (0.3)
Dyspnoea [2]	1 (0.3)	3 (1.0)	5 (1.7)	3 (1.0)
Vomiting	3 (1.0)	2 (0.7)	6 (2.0)	1 (0.3)
Pneumonitis [3]	-	4 (1.3)	5 (1.7)	1 (0.3)
Psychotic disorder	-	1 (0.3)	4 (1.3)	1 (0.3)
Nausea	2 (0.7)	4 (1.3)	3 (1.0)	1 (0.3)
Diarrhoea	-	3 (1.0)	3 (1.0)	1 (0.3)
Fatigue	1 (0.3)	2 (0.7)	3 (1.0)	1 (0.3)
Anaemia	-	2 (0.7)	3 (1.0)	1 (0.3)
Stomatitis	-	-	3 (1.0)	1 (0.3)
Hepatic failure	-	-	1 (0.3)	2 (0.7)
Dehydration	-	1 (0.3)	2 (0.7)	1 (0.3)
Urinary tract infection	1 (0.3)	-	2 (0.7)	1 (0.3)
Renal failure acute [4]	-	-	2 (0.7)	1 (0.3)
Infection	-	2 (0.7)	3 (1.0)	-
Decreased appetite	1 (0.3)	-	3 (1.0)	-
Cachexia	-	-	3 (1.0)	-

	everolimus + exemestane N = 299			
Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Jaundice	-	-	3 (1.0)	-

CTCAE = Common Terminology Criteria for Adverse Events, SAE = serious adverse event.

Only the most common grade 3 – 4 SAEs are listed. Cut off: Incidence of grade 3 – 4 SAEs ≥ 1% for preferred term. Preferred terms are listed in descending frequency of grade 3 plus grade 4 SAEs.

SAEs listed under similar preferred terms:

[1] "Pneumonia streptococcal" 1 patient (0.3%) grade 3.

[2] "Dyspnoea exertional" 2 patients (1 [0.3%] grade 2, 1 [0.3%] grade 3).

[3] "Alveolitis" 2 patients (1 [0.3%] grade 2, 1 [0.3%] grade 4); "Interstitial lung disease" 2 patients (1 [0.3%] grade 1, 1 [0.3%] grade 2).

[4] "Renal failure" 3 patients (1 [0.3%] grade 2, 2 [0.7%] grade 3).

Discontinuations

Incidence of most common AEs leading to permanent discontinuation of study treatment, by SOC and preferred term (≥ 2%) (safety set)

Primary SOC Preferred term	everolimus + exemestane N = 299 n (%)
Patients with at least 1 AE leading to discontinuation	**77 (25.8)**
Gastrointestinal disorders	**29 (9.7)**
Stomatitis [1]	13 (4.3)
Nausea	6 (2.0)
Vomiting	6 (2.0)
General disorders & administration site conditions	**13 (4.3)**
Infections & infestations	**9 (3.0)**
Investigations	**11 (3.7)**
Nervous system disorders	**10 (3.3)**
Psychiatric disorders	**8 (2.7)**
Respiratory, thoracic & mediastinal disorders	**19 (6.4)**
Dyspnoea	7 (2.3)
Pneumonitis [2]	6 (2.0)
Skin & subcutaneous tissue disorders	**8 (2.7)**

SOC = system organ class, AE = adverse event.
Only the most common AEs leading to discontinuation are listed. Cut off: Incidence ≥ 2% for SOC or preferred term.
AEs listed under similar preferred terms:
[1] "Aphthous stomatitis 1 patient (0.3%); "Mouth ulceration" 1 patient (0.3%).
[2] "Alveolitis" 1 patients (0.3%); "Interstitial lung disease" 1 patients (0.3%).
Note: The information provided in this table is driven from the Adverse Events CRF. Therefore, information about AEs leading to discontinuation of study treatment is slightly different from the information retrieved from the End of Treatment CRF.

Incidence of most common AEs requiring dose adjustment or interruption of study treatment, by SOC and preferred term (≥ 2%) (safety set)

Primary SOC Preferred term	everolimus + exemestane N = 299 n (%)
Patients with at least 1 AE req. adjust./interrupt.	**133 (44.5)**
Blood & lymphatic system disorders	**14 (4.7)**
Thrombocytopenia	7 (2.3)
Leukopenia	6 (2.0)
Gastrointestinal disorders	**65 (21.7)**
Stomatitis [1]	35 (11.7)
Diarrhoea	13 (4.3)
Nausea	11 (3.7)
Vomiting	11 (3.7)
Aphthous stomatitis	6 (2.0)
General disorders & administration site conditions	**22 (7.4)**
General physical health deterioration	7 (2.3)
Infections & infestations	**25 (8.4)**
Investigations	**14 (4.7)**
Metabolism & nutrition disorders	**7 (2.3)**
Nervous system disorders	**10 (3.3)**
Respiratory, thoracic & mediastinal disorders	**32 (10.7)**
Dyspnoea	12 (4.0)
Pneumonitis [2]	10 (3.3)
Cough	7 (2.3)
Skin & subcutaneous tissue disorders	**21 (7.0)**
Rash [3]	7 (2.3)

SOC = system organ class, AE = adverse event.
Only the most common AEs requiring dose adjustment or interruption are listed. Cut off: Incidence ≥ 2% for SOC or preferred term.

AEs listed under similar preferred terms:
[1] "Tongue ulceration" 1 patient (0.3%).
[2] "Interstitial lung disease" 1 patients (0.3%).
[3] "Rash generalised" 1 patients (0.3%).
AEs listed under similar preferred terms:
[1] "Tongue ulceration" 1 patient (0.3%).
[2] "Interstitial lung disease" 1 patients (0.3%).
[3] "Rash generalised" 1 patients (0.3%).

Other Relevant Findings

NA

Conclusion:

The present study demonstrated the efficacy of a treatment with everolimus + exemestane in a more advanced and more heavily pretreated patient population than in the BOLERO-2 phase III clinical trial. ORR and PFS were lower than in the everolimus + exemestane treatment arm of BOLERO-2 but substantially higher than in the placebo + exemestane treatment arm of BOLERO-2. This result holds true for all investigated subgroups, including the subgroups of patients with exemestane as previous therapy, patients with previous chemotherapy in metastatic setting, and patients at a late (≥ 5^{th}) therapy line.

Study treatment was accompanied by deterioration in most of the tested HRQoL scores as was to be expected in this patient population and late therapy setting. However, deterioration in a global health status/QoL score and in specific symptom scores was highest at the beginning of treatment and levelled off thereafter, and affected symptom scores were mostly known side effects of everolimus. Thus, some of the deterioration may also have resulted from side effects of study treatment.

Safety results (incidences and kind of AEs, SAEs and fatal SAEs) were in line with the known safety profile of everolimus.

Date of Clinical Trial Report

17 Nov 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

18 Nov 2014

Date of Latest Update