Sponsor

Novartis

Generic Drug Name

Everolimus

Trial Indication(s)

Breast cancer.

Protocol Number

CRAD001Y2301

Protocol Title

A randomized double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole.

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

03-Jun-2009 to 04-Dec-2014.

Reason for Termination (If applicable)applicable

Not applicable.

Study Design/Methodology

This is a multicenter, double-blind, randomized, placebo-controlled, international Phase III study evaluating treatment with everolimus (10 mg daily) versus placebo in combination with exemestane (25 mg daily) in postmenopausal women with locally advanced or metastatic ER-positive breast cancer refractory to non-steroidal aromatase inhibitors (letrozole or anastrozole).

Patients were randomized 2:1 to receive either everolimus or matching placebo in a blinded manner in addition to open-label exemestane, stratified by documented sensitivity to prior

hormonal therapy (yes versus no), and presence of visceral metastasis (yes versus no). Patients were to receive the study treatment until progression, intolerable toxicity, or consent withdrawal; further treatment after progression was at the Investigator's discretion.

Following progression or after study treatment discontinuation, patients continued to be followed for survival at least every three months for an estimated three years after randomization of the last patient (until a total of 398 deaths were recorded).

Centers

International, multicenter trial: 195 centers in 24 countries.

Publication

[Piccart M, Hortobagyi G N, Campone M, et al. (2014)] Everolimus plus exemestane for hormonereceptorpostive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Annuals of Oncology; 25(12):2357-2362.

[Baselga J, Campone M, Piccart M, et al. (2012)] Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med.; 366(6):520-529.

Objectives:

Primary objective:

- To compare the combination treatment of everolimus and exemestane to exemestane alone with respect to progression-free survival (PFS) in postmenopausal women with ER positive breast cancer that is refractory to NSAIs.

Key secondary objective:

- To compare overall survival (OS) between the two treatment arms.

Other secondary objectives:

- To evaluate the two treatment arms with respect to:
  - Overall response rate (ORR)
  - Time to deterioration of Eastern Cooperative Group performance status (ECOG PS)
  - Safety
  - Change in quality-of-life (QoL) scores over time
  - Clinical benefit rate (CBR)
- To summarize time to response and duration of response in the two treatment arms

- To characterize in a subgroup of patients the pharmacokinetics (PK) of everolimus (C_{min}, C_{2h}) when administered in combination with exemestane
- To compare the two treatment arms with respect to pre-dose concentration (C_{min}) and concentration at 2 hours post-dose (C_{2h}) of exemestane and to compare in a subgroup of patients the two treatment arms with respect to estradiol (E_2) changes from baseline

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

Everolimus was administered in accordance with a 10 mg oral daily dosing regimen (two 5 mg tablets) in conjunction with exemestane 25 mg orally daily. Batch numbers for the everolimus 5 mg tablets were: S0006, S0007, S0008, S0009, S0010, S0016, S0020, S0024, S0026, S0030 and S0036.

Statistical Methods

Progression-free and OS were analyzed using Kaplan-Meier methodology; treatment arms were compared using a stratified log-rank test and the hazard ratio estimated using a Cox proportional hazard model.

The analysis of OS was based on the data from the full analysis set, according to the treatment arms and stratum patients were randomized to at baseline. The distribution of OS was compared between the everolimus plus exemestane arm and the placebo plus exemestane arm using a stratified log-rank test at one-sided 2.5% level of significance (strata based on the stratification variables used at the time of randomization). The distribution function of OS was estimated using Kaplan-Meier method and displayed for each treatment group. The median OS along with 95% confidence intervals (CIs) was presented by two treatment arms, along with proportion of patients alive at 12, 18, 24, 30, and 36 months and the associated 95% CIs. The stratified Cox regression was used to estimate the hazard ratio (HR) of OS, along with 95% CIs (strata based on the stratification variables used at the time of randomization), where the baseline hazard functions was allowed to vary across strata.

For the sensitivity analysis, a stratified multivariate Cox proportional hazard model was fitted, adjusting the treatment difference for key potential prognostic factors including prior chemotherapy (yes vs. no), performance status (0 vs. 1, 2), bone only lesions at baseline (yes vs. no), time since first diagnosis of metastasis/recurrence to randomization ($\leq$ 6 months, >6 months), NSAI letrozole or anastrozole usage (adjuvant vs. metastatic), number of organs involved (1 vs. 2 vs. $\geq$ 3) and PgR status (positive, negative).

Overall survival was hierarchically tested in the following way: If the test of PFS (primary endpoint) was significant, OS was also tested for significance. If OS was not statistically significant, the OS endpoint was tested again at each subsequent protocol-defined interim analysis or at the final OS analysis.

All safety analyses were based on the data from the safety population. The safety summary tables included only 'on-treatment' events/assessments, that is, data collected up to 28 days since the date of last study treatment administration. Deaths, AEs, SAEs, and vital signs were listed, and those collected after 28 days from treatment discontinuation were indicated.

Adverse events were coded using the medical dictionary for regulatory activities terminology (MedDRA Version 17.1) and were assessed according to the National Cancer's Institute Common terminology criteria for adverse events, Version 3.0. Separate AE summaries were presented by primary system organ class (SOC), and preferred term. Deaths and other non-fatal SAEs were also summarized. No new safety information is provided for clinical laboratory evaluations.

Study Population: Key Inclusion/Exclusion Criteria

Adult postmenopausal women with ER-positive locally advanced or metastatic breast cancer whose disease was refractory to NSAIs and with documented recurrence or progression on last therapy for breast cancer.

Participant Flow Table

Patient disposition by treatment (Full analysis set)

	Everolimus 10mg + exemestane N=485 n (%)	Placebo + exemestane N=239 n (%)
Screened		
Randomized	485 (100.0)	239 (100.0)
Discontinued#	485 (100.0)	239 (100.0)
Adverse Event(s)	52 (10.7)	8 (3.3)
Subject withdrew consent	47 (9.7)	7 (2.9)
Administrative problems	1 (0.2)	0
Death	7 (1.4)	1 (0.4)
New cancer therapy	5 (1.0)	1 (0.4)
Disease progression	364 (75.1)	221 (92.5)
Treatment duration completed as per protocol	5 (1.0)	1 (0.4)
Protocol deviation	4 (0.8)	0

Per 'End of Treatment' page. All percentages in this section use N as the denominator.

Baseline Characteristics

Patient demographics at baseline - Full Analysis Set

Demographic variable	Everolimus plus exemestane N=485	Placebo plus exemestane N=239	All patients N=724
Age (years)			
n	485	239	724
Mean (standard deviation)	62.5 (10.31)	61.2 (9.75)	62.1 (10.14)
Median	62.0	61.0	61.0
Range	34 - 93	28 - 90	28 - 93
Age category (years) - n (%)			
< 65	290 (59.8)	159 (66.5)	449 (62.0)
≥ 65	195 (40.2)	80 (33.5)	275 (38.0)

Summary of Efficacy

Primary Outcome Result(s)

Analysis of PFS as per investigator using Kaplan-Meier methodology - Full Analysis Set

	Everolimus plus exemestane N=485	Placebo plus exemestane N=239	p-value [a]	Hazard ratio [b] [95% CI]
No. of PFS events - n (%)	202 (41.6)	157 (65.7)	<0.0001	0.43 [0.35, 0.54]
Progression	190 (39.2)	156 (65.3)		
Death [c]	12 (2.5)	1 (0.4)		
No. censored - n (%)	283 (58.4)	82 (34.3)		
Kaplan-Meier estimates [95% CI] at:				
2 months	0.87 [0.84, 0.90]	0.63 [0.56, 0.69]		
4 months	0.74 [0.69, 0.78]	0.45 [0.38, 0.52]		
6 months	0.56 [0.51, 0.62]	0.27 [0.21, 0.34]		
9 months	0.40 [0.34, 0.46]	0.15 [0.10, 0.22]		
25th percentile for PFS [95% CI]	3.78 [2.83, 4.14]	1.41 [1.38, 1.48]		
Median PFS [95% CI]	6.93 [6.44, 8.05]	2.83 [2.76, 4.14]		
75th percentile for PFS [95% CI]	12.48 [11.14, 14.00]	6.77 [5.29, 8.15]		

CI Confidence interval; PFS Progression-free survival

[a] p-value is obtained from the one-sided log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis

[b] Hazard ratio is obtained from the stratified Cox proportional hazard model

[c] Death before progression

Secondary Outcome Result(s)

Analysis of overall survival using Kaplan-Meier method (Full Analysis Set)

	Everolimus 10mg + exemestane	Placebo + exemestane		Everolimus 10mg +exemestane/ placebo +exemestane
	N=485	N=239	p-value[1]	Hazard ratio [95% CI] [2]
No. of deaths, n (%)	267 (55.1)	143 (59.8%)	0.1426	0.89 [0.73,1.10]
No. censored, n (%)	218 (44.9)	96 (40.2%)		
Kaplan-Meier estimates [95% CI] at:				
12 months	0.82 [0.79, 0.86]	0.78 [0.73, 0.83]		
18 months	0.70 [0.66, 0.74]	0.66 [0.60, 0.72]		
24 months	0.62 [0.57, 0.66]	0.53 [0.47, 0.59]		
30 months	0.51 [0.47, 0.56]	0.47 [0.40, 0.53]		
36 months	0.43 [0.39, 0.48]	0.39 [0.32, 0.46]		
25th percentile for OS [95% CI]	15.67 [13.14, 17.48]	13.63 [11.04, 16.07]		
Median OS [95% CI]	30.98 [27.96, 34.56]	26.55 [22.57, 33.08]		
75th percentile for OS [95% CI]	NA [43.63, NA]	NA [NA, NA]		

[1] One-sided P-value is obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS.
[2] Hazard ratio is obtained from stratified Cox's proportional hazard model.

Best overall response as per investigator - Full Analysis Set

Best overall response	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)	p-value [a]
Complete response (CR)	2 (0.4)	0	
Partial response (PR)	44 (9.1)	1 (0.4)	
Stable disease (SD)	340 (70.1)	140 (58.6)	
Progressive disease	48 (9.9)	75 (31.4)	
Unknown/too early to evaluate	51 (10.5)	23 (9.6)	
Response analysis			
Objective response rate (ORR) [b]	46 (9.5)	1 (0.4)	<0.0001
95% confidence interval	7.0, 12.4	0.0, 2.3	
Clinical benefit rate (CBR) [c]	162 (33.4)	43 (18.0)	<0.0001
95% confidence interval	29.2, 37.8	13.3, 23.5	

Best overall response	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)	p-value [a]

[a] p-value is obtained from the exact Cochran-Mantel-Haenszel test using a stratified version of the Cochran-Armitage permutation test
[b] Objective response rate = proportion of patients with CR or PR
[c] Clinical benefit rate = proportion of patients with CR or PR or SD ≥ 24 weeks

Time to overall response based on investigator by treatment - Full Analysis Set

	Everolimus 10mg + exemestane N=485	Placebo + exemestane N=239
No. of ORR events	46 (9.5%)	1 (0.4%)
No. censored	439 (90.5%)	238 (99.6%)
Kaplan-Meier estimates [95% CI] at:		
2 months	0.96 [0.94, 0.98]	1.00 [0.97, 1.00]
4 months	0.93 [0.91, 0.95]	1.00 [0.97, 1.00]
6 months	0.92 [0.89, 0.94]	1.00 [0.97, 1.00]
9 months	0.90 [0.88, 0.93]	1.00 [0.97, 1.00]
25th percentile for ORR [95% CI]	NA [NA, NA]	NA [NA, NA]
Median ORR [95% CI]	NA [NA, NA]	NA [NA, NA]
75th percentile for ORR [95% CI]	NA [NA, NA]	NA [NA, NA]

Duration of overall response (CR or PR) based on investigator by treatment-Full Analysis Set (Only patients with best overall response CR or PR)

	Everolimus 10mg + exemestane N=485	Placebo + exemestane N=239
No. of events	13 (2.7%)	0
No. censored	33 (6.8%)	1 (0.4%)
Kaplan-Meier estimates [95% CI] at:		
2 months	1.00 [1.00, 1.00]	NE [NE,NE]
4 months	0.85 [0.68, 0.94]	NE [NE,NE]
6 months	0.62 [0.40, 0.78]	
9 months	0.47 [0.23, 0.68]	
Median duration of response [95% CI]	8.21 [5.55, NA]	NA [NA, NA]

Analysis of time to definitive deterioration of ECOG performance status using Kaplan-Meier method by treatment-Full Analysis Set

Everolimus 10mg+exemestane N= 485	Placebo+exemestane N= 239	P-value [1]

No. of events	145 (29.9)	53 (22.2)	0.6142
Definitive deterioration	142 (29.3)	50 (20.9)	
Death	3 (0.6)	3 (1.3)	
No. censored	340 (70.1)	186 (77.8)	
Kaplan-Meier estimates			
2 months	0.84 (0.80, 0.87)	0.87 (0.82, 0.91)	
4 months	0.74 (0.70, 0.78)	0.80 (0.73, 0.85)	
6 months	0.64 (0.58, 0.69)	0.67 (0.57, 0.75)	
9 months	0.57 (0.50, 0.63)	0.47 (0.32, 0.61)	
25th percentile [95% CI]	3.71 (2.83, 4.27)	4.21 (2.83, 6.21)	
Median [95% CI]	13.83 (8.41, NA)	8.74 (7.00, NA)	
75th percentile [95% CI]	NA (15.21, NA)	NA (12.68, NA)	

Analysis of time to deterioration of PRO scores using Kaplan-Meier methodology - Full Analysis Set

EORTC QLQ-C30 domain	Everolimus plus exemestane N=485	Placebo plus exemestane N=239	p-value [a]
Deterioration in global health status/quality-of-life domain score of ≥ 5%			0.4346
No. of events - n (%)	226 (46.6)	98 (41.0)	
No. censored - n (%)	259 (53.4)	141 (59.0)	
Median time to event [95% CI] (months)	4.53 [4.17, 5.68]	4.40 [3.58, 5.85]	
Deterioration in PF domain score of ≥ 5%			0.5167
No. of events - n (%)	213 (43.9)	98 (41.0)	
No. censored - n (%)	272 (56.1)	141 (59.0)	
Median time to event [95% CI] (months)	4.83 [4.17, 6.97]	4.37 [2.83, 7.00]	
Deterioration in EF domain score of ≥ 5%			0.6270
No. of events - n (%)	198 (40.8)	83 (34.7)	
No. censored - n (%)	287 (59.2)	156 (65.3)	
Median time to event [95% CI] (months)	6.93 [5.55, 8.41]	6.93 [4.17, 7.36]	
Deterioration in SF domain score of ≥ 5%			0.3068
No. of events - n (%)	175 (36.1)	60 (25.1)	
No. censored - n (%)	310 (63.9)	179 (74.9)	
Median time to event [95% CI] (months)	8.34 [6.93, 10.87]	7.03 [5.62, NA]	

CI Confidence interval; EF Emotional functioning; EORTC European Organisation for Research and Treatment of Cancer; NA Not available; PF Physical functioning; PRO Patient-reported outcomes; SF Social functioning

[a] p-value is obtained from a two-sided stratified log-rank test

Summary of Safety

Safety Results

Grading (severity) of adverse events irrespective of relationship to study drug (with at least 2% incidence of grade 3-4 events in either group) by preferred term (Safety set)

	Everolimus 10mg + exemestane N=482			Placebo + exemestane N=238		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Preferred term	482 (100.0)	216 (44.8)	51 (10.6)	219 (92.0)	57 (23.9)	13 (5.5)
Stomatitis	287 (59.5)	39 (8.1)	0	28 (11.8)	2 (0.8)	0
Fatigue	182 (37.8)	20 (4.1)	2 (0.4)	65 (27.3)	3 (1.3)	0
Diarrhoea	173 (35.9)	11 (2.3)	1 (0.2)	44 (18.5)	2 (0.8)	0
Dyspnoea	111 (23.0)	25 (5.2)	1 (0.2)	26 (10.9)	2 (0.8)	1 (0.4)
Anaemia	105 (21.8)	35 (7.3)	3 (0.6)	12 (5.0)	2 (0.8)	1 (0.4)
Pneumonitis	79 (16.4)	15 (3.1)	0	0	0	0
Aspartate aminotransferase increased	76 (15.8)	19 (3.9)	1 (0.2)	13 (5.5)	3 (1.3)	0
Asthenia	73 (15.1)	9 (1.9)	1 (0.2)	11 (4.6)	1 (0.4)	0
Hyperglycaemia	72 (14.9)	25 (5.2)	2 (0.4)	5 (2.1)	1 (0.4)	0
Alanine aminotransferase increased	66 (13.7)	17 (3.5)	1 (0.2)	11 (4.6)	5 (2.1)	0
Thrombocytopenia	63 (13.1)	10 (2.1)	5 (1.0)	1 (0.4)	0	1 (0.4)
Gamma-glutamyltransferase increased	53 (11.0)	23 (4.8)	11 (2.3)	20 (8.4)	11 (4.6)	5 (2.1)
Hypokalaemia	41 (8.5)	14 (2.9)	2 (0.4)	4 (1.7)	3 (1.3)	0
Neutropenia	40 (8.3)	11 (2.3)	0	5 (2.1)	1 (0.4)	2 (0.8)
General physical health deterioration	16 (3.3)	7 (1.5)	4 (0.8)	1 (0.4)	0	0

- Relationship to study drug (not suspected/suspected): The temporal relationship of the clinical event to study treatment (everolimus and/or exemestane) administration makes a causal relationship unlikely or possible.

- AEs are presented in descending order of frequency of all grades according to the everolimus treatment group.

- The event with maximum severity is counted for patients who experienced multiple episodes of an event.

- Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

Summary of deaths and adverse events (Safety set)

	Everolimus 10mg + exemestane N=482	Placebo + exemestane N=238
Category	**n (%)**	**n (%)**
All deaths	289 (60.0)	154 (64.7)
On-treatment deaths [1]	22 (4.6)	4 (1.7)
Adverse events (AEs)	482 (100)	219 (92.0)
AEs suspected to be drug related	466 (96.7)	150 (63.0)
Grade 3-4 AEs	267 (55.4)	70 (29.4)
Grade 3-4 AEs Suspected to be drug related	198 (41.1)	20 (8.4)
Clinically notable AEs	459 (95.2)	125 (52.5)
Clinically notable AEs Suspected to be drug related	431 (89.4)	51 (21.4)
Serious adverse events (SAEs)	158 (32.8)	37 (15.5)
Serious adverse events (SAEs) Suspected to be drug-related	62 (12.9)	4 (1.7)
AEs leading to discontinuation	141 (29.3)	12 (5.0)
AEs leading to discontinuation Suspected to be drug-related	113 (23.4)	8 (3.4)
Other significant AEs	461 (95.6)	176 (73.9)
AEs requiring dose adjustment and/or interruption	319 (66.2)	36 (15.1)
AEs requiring additional therapy	453 (94.0)	174 (73.1)

-[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment

- Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized

- Additional therapy includes all non-drug therapy and concomitant medications

- The AE groupings consist of adverse events for which there is a specific clinical interest in connection with Everolimus or adverse events

Summary of PK:

Everolimus concentrations at Week 4 by timepoint - Safety Set

Everolimus concentrations (ng/mL)	Everolimus plus exemestane
Pre-dose (C_{min})	
n	22
Mean (standard deviation)	16.04 (9.356)
CV%	58.3
Geometric mean	14.00
Geometric CV%	55.3
Median	12.20
Range	5.7 - 38.6

Everolimus concentrations (ng/mL)	Everolimus plus exemestane
2 hours post-dose (C_{2h})	
n	24
Mean (standard deviation)	46.50 (17.954)
CV%	38.6
Geometric mean	42.52
Geometric CV%	50.4
Median	44.00
Range	8.4 - 79.2

CV Coefficient of variation

Exemestane concentrations at Week 4 by timepoint - Safety Set

Exemestane concentrations (ng/mL)	Everolimus plus exemestane	Placebo plus exemestane
Pre-dose (C_{min})		
n	34	22
Mean (standard deviation)	0.63 (0.474)	0.43 (0.376)
CV%	75.2	86.6
Geometric mean	0.54	0.37
Geometric CV%	57.3	70.1
Median	0.49	0.35
Range	0.2 - 3.0	0.0 - 1.9
Geometric mean ratio [90% CI] [a]	1.45 [1.11, 1.90]	
2 hours post-dose (C_{2h})		
n	39	22
Mean (standard deviation)	23.16 (19.805)	13.30 (11.889)
CV%	85.5	89.4
Geometric mean	16.77	9.83
Geometric CV%	111.1	124.1
Median	15.20	10.25
Range	0.5 - 96.8	0.0 - 50.8
Geometric mean ratio [90% CI] [a]	1.71 [1.12, 2.59]	

CI Confidence interval; CV Coefficient of variation

[a] Geometric mean ratio of exemestane with everolimus to those without everolimus is calculated using an analysis of variance (ANOVA) model with treatment as a fixed effect on log-transformed concentration values.

Estradiol plasma concentrations by timepoint - Safety Set

Estradiol concentrations (pg/mL)	Everolimus plus exemestane	Placebo plus exemestane
Baseline		
n	41	14
Mean (standard deviation)	5.62 (3.342)	4.09 (1.792)
CV%	59.4	43.8
Geometric mean	4.84	3.78
Geometric CV%	58.6	42.3
Median	4.78	3.93
Range	2.1 to 15.5	2.0 to 8.4
Week 4		
n	38	15
Mean (standard deviation)	3.50 (2.551)	5.17 (6.919)
CV%	72.9	133.9
Geometric mean	3.07	3.43
Geometric CV%	46.5	90.2
Median	2.71	2.40
Range	2.0 to 15.0	2.1 to 27.2
Change from baseline to Week 4		
n	27	8
Mean (standard deviation)	-2.34 (2.402)	1.72 (9.240)
CV%	-102.5	538.0
Geometric mean	0.51	2.50
Geometric CV%	78.3	431.6
Median	-2.18	-0.49
Range	-8.1 to 0.9	-5.9 to 23.4

CV Coefficient of variation

Other Relevant Findings

Not applicable.

Conclusion:

Results provide compelling evidence for the efficacy of everolimus plus exemestane in postmenopausal women with locally advanced or metastatic breast cancer, with this trial meeting its primary PFS endpoint at the interim analysis.

- Clinical benefit was evident relative to placebo plus exemestane in the form of a 57% risk reduction in PFS as per investigator assessment and a clinically meaningful 4.10-month prolongation in median PFS. Multiple supportive and sensitivity analyses demonstrated this PFS benefit to be robust and consistent across relevant prognostic categories.

- Results of the secondary efficacy endpoints were also supportive of the primary variable. Treatment with everolimus plus exemestane was associated with improved rates of objective response (9.5% versus 0.4%) and clinical benefit (33.4% versus 18.0%) relative to placebo plus exemestane. Duration of overall response ranged from 6.0+ to 66.1+ weeks for the everolimus plus exemestane arm and was 12.1+ weeks for the only patient in the placebo plus exemestane arm with a response. Time to deterioration of ECOG PS (≥ 1 point) and median times to deterioration (≥ 5%) of QLQ-C30 domain scores were similar for the two treatment arms.
- Results from the final OS analysis continue to support the clinical benefit of adding everolimus to exemestane compared to exemestane alone. Everolimus plus exemestane prolongs OS, and the 4.43 month improvement in median OS duration compared to the placebo plus exemestane arm is considered to be clinically relevant and meaningful.
- Following co-administration with everolimus, average exemestane C_{min} and C_{2h} were 45% and 71% higher than the corresponding exemestane monotherapy values. These increases in exemestane concentrations are considered unlikely to have had a major impact on either efficacy or safety as plasma estrogen (estradiol, estrone, and estrone sulfate) suppression was seen starting at a 5-mg daily dose of exemestane, with a maximum suppression of ≥ 85% to 95% achieved at a 25-mg dose and experience with repeated doses of up to 200 mg exemestane daily have demonstrated only a moderate increase in AEs.
- No unexpected or new safety concerns were identified, and everolimus in combination with exemestane was associated with a manageable safety profile that is consistent with approved indication in this setting and previous experience in the oncology setting.

Date of Clinical Trial Report

Primary CSR: 24-Oct-2011

Final OS CSR: 07-Apr-2014

Close-out CSR: 30-Apr-2015