NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Everolimus

Trial Indication(s)

HER2 positive locally advanced or metastatic breast cancer

Protocol Number

CRAD001J2301

Protocol Title

A Randomized Phase III, Double-Blind, Placebo-Controlled Multicenter Trial of Everolimus in Combination with Trastuzumab and Paclitaxel, as First Line Therapy in Women with HER2 Positive Locally Advanced or Metastatic Breast Cancer

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: September 2009 (Actual)
Primary Completion Date: May 2014 (Actual)
Study Completion Date: October 2017 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a randomized (2:1) Phase III, double-blind, placebo-controlled, multicenter, two-arm international study of everolimus (10 mg daily) in combination with paclitaxel (80 mg/m2 weekly) and trastuzumab (2 mg/kg weekly) versus placebo in combination with the same dose of weekly paclitaxel and trastuzumab, as first line therapy for the treatment of HER2-positive advanced breast cancer (ABC) in women who had not previously received chemotherapy or biologic agents for ABC.
Novartis recommended to terminate the study as the primary objectives, PFS for this study (30-May-2014 cut-off date) were not met in either the full population or in the HR-negative subpopulation. Based on protocol amendment 4, Novartis in agreement with the trial scientific steering committee, decided to proceed with one final exploratory OS analysis at the time of the recommended study termination. The final exploratory overall survival (OS) analysis was presented in the CSR for OS analyses up to data cut-off date 31-Dec-2015. This report only presents limited cumulative safety analyses for all patients randomized in the study up to the LPLV (23-Oct-2017).

Centers

179 centers in 27 countries: South Africa(3), Venezuela(1), United States(41), Taiwan(5), Turkey(5), Russia(7), Peru(2), Mexico(2), Lebanon(3), Korea, Republic of(4), Japan(15), Italy(5), Ireland(4), Hong Kong(3), Greece(6), United Kingdom(3), France(8), Egypt(3), Germany(11), Colombia(4), China(10), Switzerland(3), Canada(4), Brazil(6), Belgium(7), Australia(4), Argentina(10)

Objectives:

The two primary objectives were to compare PFS between the combination treatment of everolimus, trastuzumab, paclitaxel, and the combination treatment of placebo, trastuzumab, paclitaxel in patients with HER2-overexpressing, unresectable, locally advanced or metastatic breast cancer (MBC) in the:

- Full population, and
- Hormone receptor (HR)-negative subpopulation.

The two key secondary objectives were to compare overall survival (OS) between the combination treatment of everolimus, trastuzumab, paclitaxel and the combination treatment of placebo, trastuzumab, paclitaxel in the:

- Full population, and
- HR-negative subpopulation.

Other secondary objectives: were to evaluate 1) the following efficacy endpoints in both the full population and HR-negative subpopulation: overall response rate (ORR), time to deterioration of Eastern Cooperative Oncology Group performance status (ECOG PS), clinical benefit rate (CBR), time to Novartis response, and duration of response 2) safety in the full population and in the HR-negative subpopulation 3) the impact of co-administration of everolimus on paclitaxel pharmacokinetics (PK) in the presence of trastuzumab and to evaluate the impact of co-administration of paclitaxel on everolimus PK in the presence of trastuzumab.

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

Everolimus was administered in a continuous oral daily dosing of 10 mg (two 5-mg tablets).

Commercially available trastuzumab (2 mg/kg weekly) and paclitaxel (80 mg/m2 weekly) were used (intravenous) according to the Investigator country guidelines.

Statistical Methods

There were two planned PFS analyses: an interim analysis after at least 309 of the total events were reported in the full population, and a final analysis after 420 PFS events were observed in the full population. At the time of the interim analyses, PFS was tested only in the full population. At the time of the final PFS analyses, PFS was tested both in the full population and HR-negative subpopulation. Group sequential design was implemented using α-spending function with O'Brien-Fleming type stopping boundary for the two planned PFS analyses. A Lan and DeMets (1983) with O'Brien-Fleming type alpha spending functions were defined independently for the full population and the HR-negative subpopulation, each at the overall alpha level as allocated by weighted Hochberg procedure with unequal weights (80% to full population and 20% to HR- subpopulation). Survival distribution of PFS for each treatment arm was estimated using the Kaplan-Meier method. The stratified Cox regression model (using the baseline stratification factors) was used to estimate the HR for risk reduction of PFS, along with 95% confidence interval (CI).

A hierarchical testing strategy was used for the key secondary endpoint OS, where OS was to be statistically evaluated and interpreted only if PFS was significantly different between the two treatment arms in the respective population (full population and/or HR-negative subpopulation).

A stratified Cochran-Mantel-Haenszel test at the one-sided level of significance of 0.025 was used to compare the two treatment arms with respect to the ORR and CBR.
Safety was analyzed for all patients who received at least one dose of study medication according to the medication actually received. Demographic and baseline disease characteristics were presented by treatment group in the Full Analysis Set for all randomized patients according to the treatment to which they were randomized (intent to treat principle). Exposure-related and safety-related data were summarized overall and by treatment group in the Safety set.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
• Adult Women (≥ 18 years old).
• Histologically or cytologically confirmed invasive breast carcinoma with local recurrence or radiological evidence of metastatic disease.
• Must have at least one lesion that can be accurately measured or bone lesions in the absence of measurable disease.
• HER2+ patients by local laboratory testing (IHC 3+ staining or in situ hybridization positive).
• Prior trastuzumab and/or chemotherapy (taxanes included) as neo-adjuvant or adjuvant treatment is allowed but should be discontinued > 12 months prior to randomization.
• Prior treatment for breast cancer with endocrine therapy (adjuvant or metastatic settings) is allowed but should be discontinued at randomization. Patients treated with bisphosphonates at entry or who start bisphosphonates during study may continue this therapy during protocol treatment.
• Documentation of negative pregnancy test.
• Organ functions at time of inclusion.

Exclusion Criteria:
• Prior mTOR inhibitors for the treatment of cancer.
• Other anticancer therapy for locally advanced or metastatic breast cancer except for prior hormonal therapy.
• Patients with only non-measurable lesions other than bone metastasis (e.g. pleural effusion, ascites, etc).
• Radiotherapy to ≥ 25% of the bone marrow within 4 weeks prior to randomization
• History of central nervous system metastasis.
• Impairment of gastrointestinal (GI) function or GI disease or active ulceration of the upper gastrointestinal tract.
• Serious peripheral neuropathy.
• Cardiac disease or dysfunction.
• Uncontrolled hypertension.
• HIV.

• Pregnant,

Participant Flow Table

Overall Study

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Started	480	239
Untreated	8	1
Completed	0	0
Not Completed	480	239
Untreated	8	1
Adverse Event	63	11
Abnormal test procedure result(s)	1	0
Disease progression	259	162
New cancer therapy	25	7
Protocol Violation	5	2
Withdrawal by Subject	66	33
Lost to Follow-up	2	0
Administrative problems	39	23
Death	12	0

Baseline Characteristics

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab	Total
Number of Participants [units: participants]	480	239	719
Age Continuous (units: Years) Mean ± Standard Deviation			
	53.4±11.46	52.1±11.63	53.0±11.53
Sex: Female, Male (units:) Count of Participants (Not Applicable)			
Female	480	239	719
Male	0	0	0
Race/Ethnicity, Customized (units:) Count of Participants (Not Applicable)			
Caucasian	214	97	311
Black	26	12	38
Asian	198	105	303
Native American	3	0	3
Other	39	25	64

Summary of Efficacy

Primary Outcome Result(s)

Progression-free Survival (PFS) per Investigators' assessment based on local radiology review - Full population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	480	239
Progression-free Survival (PFS) per Investigators' assessment based on local radiology review - Full population (units: months) Median (95% Confidence Interval)		
	14.95 (14.55 to 17.91)	14.49 (12.29 to 17.08)

Statistical Analysis

Groups	Everolimus + Paclitaxel + Trastuzumab, Placebo + Paclitaxel + Trastuzumab
P Value	0.1166
Method	Log Rank
Hazard Ratio (HR)	0.89

95 % Confidence Interval 2-Sided	0.73 to 1.08

Progression-free Survival (PFS) per Investigators' assessment based on local radiology review - (hormone receptor (HR)-negative population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	208	103
Progression-free Survival (PFS) per Investigators' assessment based on local radiology review - (hormone receptor (HR)-negative population (units: Months) Median (95% Confidence Interval)		
	20.27 (14.95 to 24.08)	13.08 (10.05 to 16.56)

Statistical Analysis

Groups	Everolimus + Paclitaxel + Trastuzumab, Placebo + Paclitaxel + Trastuzumab
P Value	0.0049
Method	Log Rank

Hazard Ratio (HR)	0.66
95 % Confidence Interval 2-Sided	0.48 to 0.91

Secondary Outcome Result(s)

Overall Survival (OS) - Full Population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	480	239
Overall Survival (OS) - Full Population (units: Months) Median (95% Confidence Interval)		
	48.56 (40.94 to 58.94)	49.97 (40.84 to N/A)[1]

Overall Survival (OS) - HR-negative population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	208	103
Overall Survival (OS) - HR-negative population (units: Months)		

Median (95% Confidence Interval)		
	56.97 (44.09 to N/A)[1]	41.63 (34.83 to N/A)[1]

Overall response rate (ORR) - Full Population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	480	239
Overall response rate (ORR) - Full Population (units: Percentage of participants) Number (95% Confidence Interval)		
	67.1 (62.7 to 71.3)	69.0 (62.8 to 74.8)

Statistical Analysis

Groups	Everolimus + Paclitaxel + Trastuzumab, Placebo + Paclitaxel + Trastuzumab
P Value	0.7276
Method	Other Exact Cochran-Mantel-Haenzel chi-square

Overall response rate (ORR) - HR-negative population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	208	103
Overall response rate (ORR) - HR-negative population (units: Percentage of participants) Number (95% Confidence Interval)		
	73.1 (66.5 to 79.0)	70.9 (61.1 to 79.4)

Statistical Analysis

Groups	Everolimus + Paclitaxel + Trastuzumab, Placebo + Paclitaxel + Trastuzumab
P Value	0.4085
Method	Other Exact Cochran-Mantel-Haenzel chi-square

Clinical benefit rate (CBR) equal to or greater than 24 weeks - Full Population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	480	239
Clinical benefit rate (CBR) equal to or greater		

than 24 weeks - Full Population (units: Percentage of participants) Number (95% Confidence Interval)		
	75.8 (71.7 to 79.6)	81.2 (75.6 to 85.9)

Statistical Analysis

Groups	Everolimus + Paclitaxel + Trastuzumab, Placebo + Paclitaxel + Trastuzumab
P Value	0.9573
Method	Other Exact Cochran-Mantel-Haenzel chi-square

Clinical benefit rate (CBR) equal to or greater than 24 weeks - HR-negative Population

	Everolimus + Paclitaxel + Trastuzumab	**Placebo + Paclitaxel + Trastuzumab**
Number of Participants Analyzed [units: participants]	208	103
Clinical benefit rate (CBR) equal to or greater than 24 weeks - HR-negative Population (units: Percentage of participants) Number (95% Confidence Interval)		
	78.8 (72.7 to 84.2)	79.6 (70.5 to 86.9)

Statistical Analysis

Groups	Everolimus + Paclitaxel + Trastuzumab, Placebo + Paclitaxel + Trastuzumab
P Value	0.6382
Method	Other Exact Cochran-Mantel-Haenzel chi-square

Time to overall response based on Investigator - Full Population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	480	239
Time to overall response based on Investigator - Full Population (units: months) Median (95% Confidence Interval)		
	2.10 (2.00 to 3.58)	2.00 (1.94 to 2.27)

Time to overall response based on Investigator - HR-negative Population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	208	103

Time to overall response based on Investigator - HR-negative Population (units: months) Median (95% Confidence Interval)		
	1.94 (1.87 to 2.00)	1.97 (1.87 to 3.58)

Overall Response (OR) - Full Population

	Everolimus + Paclitaxel + Trastuzumab	**Placebo + Paclitaxel + Trastuzumab**
Number of Participants Analyzed [units: participants]	480	239
Overall Response (OR) - Full Population (units: Percentage of participants)		
Complete Response (CR)	5.6	5.9
Partial Response (PR)	61.5	63.2

Overall Response (OR) - HR-negative Population

	Everolimus + Paclitaxel + Trastuzumab	**Placebo + Paclitaxel + Trastuzumab**
Number of Participants Analyzed [units: participants]	208	103
Overall Response (OR) - HR-negative Population (units: Percentage of participants)		
Complete Response (CR)	7.7	2.9

Partial Response (PR)	65.4	68.0

Everolimus blood level concentrations at steady states for everolimus

	Everolimus 10 mg/day	Everolimus 5 mg/day
Number of Participants Analyzed [units: participants]	60	21
Everolimus blood level concentrations at steady states for everolimus (units: ng/mL) Mean ± Standard Deviation		
Pre-dose (Cmin) @ C2D1 (n = 54, 14)	14.380 ± 10.0169	7.959 ± 8.1546
2 hours post administration (C2h) @ C2D1 (n = 60, 17)	44.485 ± 22.1986	23.449 ± 10.4112
Pre-dose (Cmin) @ C2D15 (n = 44, 17)	13.206 ± 9.9821	5.473 ± 3.9690
2 hours post administration (C2h) @ C2D15 (n = 44, 21)	43.494 ± 21.5940	20.329 ± 7.9518
Pre-dose (Cmin) @ C2D22 (n = 40, 17)	13.432 ± 13.2782	7.494 ± 5.8503
2 hours post administration (C2h) @ C2D22 (n = 48, 21)	43.947 ± 28.0107	22.192 ± 10.9277

Paclitaxel plasma concentrations

	Everolimus	Everolimus Placebo

Number of Participants Analyzed [units: participants]	91	43
Paclitaxel plasma concentrations (units: ng/mL) Mean ± Standard Deviation		
Pre-infusion (Cmin) @ C2D15 (n = 91, 43)	1.424 ± 5.8645	0 ± 0
End of infusion (Cmax) @ C2D15 (n = 65, 33)	5159.338 ± 15473.636	4296.697 ± 7431.0799

Trastuzumab serum concentrations

	Everolimus + trastuzumab	Everolimus Placebo
Number of Participants Analyzed [units: participants]	98	54
Trastuzumab serum concentrations (units: microgram/ml) Mean ± Standard Deviation		
Pre-infusion (Cmin) @ C4D1 (n = 98, 54)	26.606 ± 9.6548	29.180 ± 12.1252
End of infusion (Cmax) @ C4D1 (n = 83, 46)	64.296 ± 23.4635	67.643 ± 20.8852

Time to deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score - Full Population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	480	239

Time to deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score - Full Population (units: months) Median (95% Confidence Interval)		
	39.20 (31.31 to N/A)[]	N/A (30.39 to N/A)[]

Time to deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score - HR-negative Population

	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Number of Participants Analyzed [units: participants]	208	103
Time to deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score - HR-negative Population (units: months) Median (95% Confidence Interval)		
	N/A (25.56 to N/A)[]	N/A (26.91 to N/A)[]

Summary of Safety

Safety Results

All-Cause Mortality

	Everolimus+ Paclitaxel+ Trastuzumab N = 472	Placebo+ Paclitaxel+ Trastuzumab N = 238
Total participants affected	23 (4.87%)	2 (0.84%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until 30 days after Last Patient Last Visit.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment

	Everolimus+ Paclitaxel+ Trastuzumab N = 472	Placebo+ Paclitaxel+ Trastuzumab N = 238
Total participants affected	173 (36.65%)	40 (16.81%)
Blood and lymphatic system disorders		
Anaemia	6 (1.27%)	0 (0.00%)

Febrile neutropenia	4 (0.85%)	1 (0.42%)
Iron deficiency anaemia	1 (0.21%)	0 (0.00%)
Leukopenia	2 (0.42%)	0 (0.00%)
Neutropenia	2 (0.42%)	2 (0.84%)
Thrombocytopenia	4 (0.85%)	0 (0.00%)
Cardiac disorders		
Acute myocardial infarction	1 (0.21%)	0 (0.00%)
Aortic valve incompetence	0 (0.00%)	1 (0.42%)
Atrial fibrillation	2 (0.42%)	0 (0.00%)
Cardiac arrest	1 (0.21%)	0 (0.00%)
Cardiac failure	1 (0.21%)	0 (0.00%)
Cardiac failure congestive	2 (0.42%)	0 (0.00%)
Cardiomyopathy	1 (0.21%)	0 (0.00%)
Cardio-respiratory arrest	1 (0.21%)	0 (0.00%)
Left ventricular dysfunction	1 (0.21%)	1 (0.42%)
Pericardial effusion	1 (0.21%)	0 (0.00%)
Sinus tachycardia	1 (0.21%)	0 (0.00%)
Supraventricular tachycardia	1 (0.21%)	0 (0.00%)
Tachycardia	2 (0.42%)	0 (0.00%)
Ventricular tachycardia	1 (0.21%)	0 (0.00%)
Ear and labyrinth disorders		
Vertigo	2 (0.42%)	0 (0.00%)

Eye disorders		
Cataract	1 (0.21%)	0 (0.00%)
Diplopia	2 (0.42%)	0 (0.00%)
Ocular surface disease	1 (0.21%)	0 (0.00%)
Strabismus	1 (0.21%)	0 (0.00%)
Gastrointestinal disorders		
Abdominal pain	2 (0.42%)	1 (0.42%)
Anal fissure	1 (0.21%)	0 (0.00%)
Ascites	1 (0.21%)	0 (0.00%)
Colitis	1 (0.21%)	0 (0.00%)
Diarrhoea	5 (1.06%)	1 (0.42%)
Dysphagia	1 (0.21%)	0 (0.00%)
Enteritis	0 (0.00%)	1 (0.42%)
Gastric haemorrhage	1 (0.21%)	1 (0.42%)
Gastritis	2 (0.42%)	0 (0.00%)
Gastritis erosive	1 (0.21%)	0 (0.00%)
Gastrointestinal haemorrhage	1 (0.21%)	0 (0.00%)
Gastrointestinal toxicity	1 (0.21%)	0 (0.00%)
Haemorrhoids	2 (0.42%)	0 (0.00%)
Intestinal obstruction	0 (0.00%)	1 (0.42%)
Intussusception	1 (0.21%)	0 (0.00%)
Large intestine perforation	1 (0.21%)	0 (0.00%)
Melaena	1 (0.21%)	0 (0.00%)
Oesophageal perforation	1 (0.21%)	0 (0.00%)

Oesophageal stenosis	1 (0.21%)	0 (0.00%)
Peritoneal haemorrhage	1 (0.21%)	0 (0.00%)
Rectal haemorrhage	2 (0.42%)	0 (0.00%)
Stomatitis	10 (2.12%)	0 (0.00%)
Upper gastrointestinal haemorrhage	1 (0.21%)	0 (0.00%)
Vomiting	2 (0.42%)	1 (0.42%)
General disorders and administration site conditions		
Asthenia	1 (0.21%)	0 (0.00%)
Calcinosis	0 (0.00%)	1 (0.42%)
Catheter site related reaction	1 (0.21%)	0 (0.00%)
Chest discomfort	1 (0.21%)	0 (0.00%)
Chills	1 (0.21%)	0 (0.00%)
Fatigue	2 (0.42%)	0 (0.00%)
General physical health deterioration	1 (0.21%)	0 (0.00%)
Generalised oedema	1 (0.21%)	0 (0.00%)
Incarcerated hernia	0 (0.00%)	1 (0.42%)
Influenza like illness	1 (0.21%)	0 (0.00%)
Multiple organ dysfunction syndrome	1 (0.21%)	0 (0.00%)
Oedema peripheral	0 (0.00%)	1 (0.42%)
Peripheral swelling	1 (0.21%)	0 (0.00%)
Pyrexia	12 (2.54%)	2 (0.84%)
Hepatobiliary disorders		

Cholecystitis	0 (0.00%)	1 (0.42%)
Cholecystitis acute	1 (0.21%)	0 (0.00%)
Drug-induced liver injury	1 (0.21%)	0 (0.00%)
Hepatic failure	1 (0.21%)	0 (0.00%)
Hepatic function abnormal	3 (0.64%)	0 (0.00%)
Hepatitis acute	1 (0.21%)	0 (0.00%)
Immune system disorders		
Anaphylactic shock	1 (0.21%)	0 (0.00%)
Drug hypersensitivity	1 (0.21%)	0 (0.00%)
Infections and infestations		
Acute sinusitis	1 (0.21%)	0 (0.00%)
Appendicitis	1 (0.21%)	0 (0.00%)
Breast abscess	1 (0.21%)	0 (0.00%)
Bronchitis	1 (0.21%)	1 (0.42%)
Cellulitis	5 (1.06%)	4 (1.68%)
Clostridium colitis	1 (0.21%)	0 (0.00%)
Device related infection	10 (2.12%)	2 (0.84%)
Fungal infection	1 (0.21%)	0 (0.00%)
Furuncle	1 (0.21%)	0 (0.00%)
Gastroenteritis	1 (0.21%)	0 (0.00%)
Herpes zoster	1 (0.21%)	1 (0.42%)
Klebsiella infection	0 (0.00%)	1 (0.42%)
Lower respiratory tract infection	1 (0.21%)	0 (0.00%)

Lower respiratory tract infection fungal	1 (0.21%)	0 (0.00%)
Lung infection pseudomonal	1 (0.21%)	0 (0.00%)
Lymphangitis	2 (0.42%)	0 (0.00%)
Mastitis	1 (0.21%)	1 (0.42%)
Neutropenic sepsis	1 (0.21%)	0 (0.00%)
Peritonitis	1 (0.21%)	0 (0.00%)
Peritonitis bacterial	1 (0.21%)	0 (0.00%)
Pneumocystis jirovecii pneumonia	3 (0.64%)	0 (0.00%)
Pneumonia	22 (4.66%)	0 (0.00%)
Pneumonia klebsiella	2 (0.42%)	0 (0.00%)
Pneumonia pneumococcal	1 (0.21%)	0 (0.00%)
Pneumonia streptococcal	1 (0.21%)	0 (0.00%)
Post procedural infection	0 (0.00%)	1 (0.42%)
Pulmonary tuberculoma	1 (0.21%)	0 (0.00%)
Pyelonephritis	1 (0.21%)	0 (0.00%)
Rash pustular	1 (0.21%)	0 (0.00%)
Respiratory tract infection	2 (0.42%)	0 (0.00%)
Salmonellosis	0 (0.00%)	1 (0.42%)
Sepsis	5 (1.06%)	1 (0.42%)
Septic shock	1 (0.21%)	1 (0.42%)
Skin infection	1 (0.21%)	0 (0.00%)
Subdiaphragmatic abscess	0 (0.00%)	1 (0.42%)

Upper respiratory tract infection	4 (0.85%)	1 (0.42%)
Urinary tract infection	7 (1.48%)	0 (0.00%)
Urosepsis	2 (0.42%)	0 (0.00%)
Wound infection	1 (0.21%)	0 (0.00%)
Injury, poisoning and procedural complications		
Fall	1 (0.21%)	0 (0.00%)
Femur fracture	2 (0.42%)	0 (0.00%)
Foot fracture	1 (0.21%)	0 (0.00%)
Forearm fracture	1 (0.21%)	0 (0.00%)
Fractured ischium	0 (0.00%)	1 (0.42%)
Fractured sacrum	1 (0.21%)	0 (0.00%)
Hip fracture	1 (0.21%)	0 (0.00%)
Humerus fracture	1 (0.21%)	0 (0.00%)
Infusion related reaction	1 (0.21%)	3 (1.26%)
Injury	1 (0.21%)	0 (0.00%)
Muscle rupture	1 (0.21%)	0 (0.00%)
Post procedural haemorrhage	1 (0.21%)	0 (0.00%)
Spinal fracture	1 (0.21%)	0 (0.00%)
Subarachnoid haemorrhage	1 (0.21%)	0 (0.00%)
Thoracic vertebral fracture	1 (0.21%)	0 (0.00%)
Investigations		

Alanine aminotransferase increased	3 (0.64%)	0 (0.00%)
Aspartate aminotransferase increased	3 (0.64%)	0 (0.00%)
Blood potassium decreased	1 (0.21%)	0 (0.00%)
Haemoglobin decreased	1 (0.21%)	0 (0.00%)
Weight decreased	2 (0.42%)	0 (0.00%)
Metabolism and nutrition disorders		
Appetite disorder	1 (0.21%)	0 (0.00%)
Decreased appetite	3 (0.64%)	0 (0.00%)
Dehydration	7 (1.48%)	0 (0.00%)
Diabetic ketoacidosis	1 (0.21%)	0 (0.00%)
Hyperglycaemia	6 (1.27%)	0 (0.00%)
Hyperkalaemia	1 (0.21%)	0 (0.00%)
Hypertriglyceridaemia	1 (0.21%)	0 (0.00%)
Hypoalbuminaemia	1 (0.21%)	0 (0.00%)
Hypocalcaemia	3 (0.64%)	0 (0.00%)
Hypokalaemia	3 (0.64%)	0 (0.00%)
Hypomagnesaemia	1 (0.21%)	0 (0.00%)
Hyponatraemia	1 (0.21%)	0 (0.00%)
Hypophosphataemia	1 (0.21%)	0 (0.00%)
Musculoskeletal and connective tissue disorders		
Back pain	2 (0.42%)	1 (0.42%)

Bone pain	0 (0.00%)	1 (0.42%)
Hypercreatinaemia	1 (0.21%)	0 (0.00%)
Musculoskeletal pain	1 (0.21%)	0 (0.00%)
Osteonecrosis of jaw	0 (0.00%)	3 (1.26%)
Nervous system disorders		
Ataxia	0 (0.00%)	1 (0.42%)
Cerebral artery embolism	0 (0.00%)	1 (0.42%)
Cerebral infarction	1 (0.21%)	0 (0.00%)
Cerebrovascular accident	2 (0.42%)	0 (0.00%)
Depressed level of consciousness	1 (0.21%)	0 (0.00%)
Disturbance in attention	1 (0.21%)	0 (0.00%)
Dizziness	5 (1.06%)	0 (0.00%)
Encephalopathy	0 (0.00%)	1 (0.42%)
Headache	3 (0.64%)	1 (0.42%)
Hemiparesis	1 (0.21%)	0 (0.00%)
Hepatic encephalopathy	1 (0.21%)	0 (0.00%)
Hypersomnia	0 (0.00%)	1 (0.42%)
Lethargy	1 (0.21%)	0 (0.00%)
Loss of consciousness	1 (0.21%)	0 (0.00%)
Nervous system disorder	0 (0.00%)	1 (0.42%)
Neuralgia	1 (0.21%)	0 (0.00%)
Peripheral sensory neuropathy	1 (0.21%)	0 (0.00%)

Sciatica	1 (0.21%)	0 (0.00%)
Seizure	2 (0.42%)	2 (0.84%)
Spinal cord compression	1 (0.21%)	0 (0.00%)
Syncope	1 (0.21%)	0 (0.00%)
Transient ischaemic attack	0 (0.00%)	1 (0.42%)
Pregnancy, puerperium and perinatal conditions		
Abortion spontaneous	1 (0.21%)	0 (0.00%)
Product issues		
Thrombosis in device	1 (0.21%)	0 (0.00%)
Psychiatric disorders		
Confusional state	3 (0.64%)	1 (0.42%)
Conversion disorder	1 (0.21%)	0 (0.00%)
Depression	1 (0.21%)	0 (0.00%)
Panic attack	1 (0.21%)	0 (0.00%)
Renal and urinary disorders		
Acute kidney injury	4 (0.85%)	1 (0.42%)
Cystitis haemorrhagic	1 (0.21%)	0 (0.00%)
Proteinuria	1 (0.21%)	0 (0.00%)
Renal impairment	1 (0.21%)	0 (0.00%)
Urinary retention	1 (0.21%)	0 (0.00%)
Reproductive system and breast disorders		
Breast pain	0 (0.00%)	1 (0.42%)
Breast ulceration	0 (0.00%)	1 (0.42%)

Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome	2 (0.42%)	0 (0.00%)
Acute respiratory failure	1 (0.21%)	0 (0.00%)
Bronchiectasis	1 (0.21%)	0 (0.00%)
Cough	0 (0.00%)	1 (0.42%)
Dyspnoea	12 (2.54%)	1 (0.42%)
Epistaxis	1 (0.21%)	0 (0.00%)
Haemoptysis	1 (0.21%)	0 (0.00%)
Hypoxia	1 (0.21%)	0 (0.00%)
Interstitial lung disease	7 (1.48%)	0 (0.00%)
Lung infiltration	1 (0.21%)	0 (0.00%)
Pharyngeal inflammation	1 (0.21%)	0 (0.00%)
Pleural effusion	1 (0.21%)	0 (0.00%)
Pleuritic pain	1 (0.21%)	0 (0.00%)
Pneumonitis	21 (4.45%)	0 (0.00%)
Pulmonary artery thrombosis	0 (0.00%)	1 (0.42%)
Pulmonary embolism	2 (0.42%)	0 (0.00%)
Pulmonary oedema	3 (0.64%)	0 (0.00%)
Respiratory arrest	2 (0.42%)	0 (0.00%)
Respiratory distress	1 (0.21%)	0 (0.00%)
Respiratory failure	5 (1.06%)	0 (0.00%)
Skin and subcutaneous tissue disorders		
Angioedema	1 (0.21%)	0 (0.00%)

Diabetic ulcer	1 (0.21%)	0 (0.00%)
Vascular disorders		
Aortic dissection	0 (0.00%)	1 (0.42%)
Deep vein thrombosis	1 (0.21%)	0 (0.00%)
Hypotension	2 (0.42%)	0 (0.00%)
Hypovolaemic shock	1 (0.21%)	0 (0.00%)
Jugular vein thrombosis	1 (0.21%)	0 (0.00%)
Lymphoedema	1 (0.21%)	0 (0.00%)
Shock	1 (0.21%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until 30 days after Last Patient Last Visit.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Everolimus+ Paclitaxel+ Trastuzumab N = 472	**Placebo+ Paclitaxel+ Trastuzumab N = 238**
Total participants affected	466 (98.73%)	236 (99.16%)
Blood and lymphatic system disorders		
Anaemia	143 (30.30%)	38 (15.97%)

Leukopenia	71 (15.04%)	24 (10.08%)
Neutropenia	177 (37.50%)	59 (24.79%)
Thrombocytopenia	46 (9.75%)	6 (2.52%)
Cardiac disorders		
Left ventricular dysfunction	32 (6.78%)	10 (4.20%)
Gastrointestinal disorders		
Abdominal pain	71 (15.04%)	29 (12.18%)
Abdominal pain upper	55 (11.65%)	26 (10.92%)
Aphthous ulcer	25 (5.30%)	4 (1.68%)
Constipation	101 (21.40%)	51 (21.43%)
Diarrhoea	267 (56.57%)	112 (47.06%)
Dyspepsia	50 (10.59%)	26 (10.92%)
Haemorrhoids	32 (6.78%)	7 (2.94%)
Mouth ulceration	60 (12.71%)	14 (5.88%)
Nausea	154 (32.63%)	83 (34.87%)
Stomatitis	315 (66.74%)	77 (32.35%)
Toothache	35 (7.42%)	21 (8.82%)
Vomiting	122 (25.85%)	55 (23.11%)
General disorders and administration site conditions		
Asthenia	94 (19.92%)	41 (17.23%)
Chills	29 (6.14%)	6 (2.52%)
Fatigue	168 (35.59%)	87 (36.55%)
Oedema peripheral	156 (33.05%)	59 (24.79%)

Pain	28 (5.93%)	12 (5.04%)
Peripheral swelling	30 (6.36%)	10 (4.20%)
Pyrexia	181 (38.35%)	63 (26.47%)
Infections and infestations		
Cellulitis	28 (5.93%)	8 (3.36%)
Influenza	36 (7.63%)	24 (10.08%)
Nasopharyngitis	90 (19.07%)	47 (19.75%)
Paronychia	26 (5.51%)	8 (3.36%)
Pharyngitis	25 (5.30%)	5 (2.10%)
Pneumonia	33 (6.99%)	10 (4.20%)
Rhinitis	30 (6.36%)	14 (5.88%)
Upper respiratory tract infection	67 (14.19%)	34 (14.29%)
Urinary tract infection	56 (11.86%)	17 (7.14%)
Investigations		
Alanine aminotransferase increased	95 (20.13%)	45 (18.91%)
Aspartate aminotransferase increased	72 (15.25%)	29 (12.18%)
Ejection fraction decreased	35 (7.42%)	15 (6.30%)
Haemoglobin decreased	41 (8.69%)	8 (3.36%)
Neutrophil count decreased	44 (9.32%)	23 (9.66%)
Weight decreased	99 (20.97%)	13 (5.46%)
Weight increased	19 (4.03%)	26 (10.92%)

White blood cell count decreased	34 (7.20%)	14 (5.88%)
Metabolism and nutrition disorders		
Decreased appetite	110 (23.31%)	36 (15.13%)
Hypercholesterolaemia	88 (18.64%)	23 (9.66%)
Hyperglycaemia	58 (12.29%)	13 (5.46%)
Hypertriglyceridaemia	68 (14.41%)	17 (7.14%)
Hypocalcaemia	24 (5.08%)	4 (1.68%)
Hypokalaemia	68 (14.41%)	9 (3.78%)
Musculoskeletal and connective tissue disorders		
Arthralgia	80 (16.95%)	41 (17.23%)
Back pain	72 (15.25%)	42 (17.65%)
Bone pain	30 (6.36%)	14 (5.88%)
Muscle spasms	33 (6.99%)	9 (3.78%)
Musculoskeletal pain	37 (7.84%)	17 (7.14%)
Myalgia	78 (16.53%)	45 (18.91%)
Pain in extremity	86 (18.22%)	39 (16.39%)
Nervous system disorders		
Dizziness	74 (15.68%)	37 (15.55%)
Dysgeusia	59 (12.50%)	24 (10.08%)
Headache	130 (27.54%)	70 (29.41%)
Hypoaesthesia	61 (12.92%)	36 (15.13%)
Neuropathy peripheral	136 (28.81%)	58 (24.37%)
Neurotoxicity	40 (8.47%)	24 (10.08%)

Paraesthesia	35 (7.42%)	25 (10.50%)
Peripheral sensory neuropathy	61 (12.92%)	37 (15.55%)
Psychiatric disorders		
Anxiety	31 (6.57%)	12 (5.04%)
Depression	23 (4.87%)	12 (5.04%)
Insomnia	78 (16.53%)	39 (16.39%)
Renal and urinary disorders		
Dysuria	40 (8.47%)	9 (3.78%)
Reproductive system and breast disorders		
Breast pain	26 (5.51%)	12 (5.04%)
Respiratory, thoracic and mediastinal disorders		
Cough	191 (40.47%)	80 (33.61%)
Dysphonia	22 (4.66%)	14 (5.88%)
Dyspnoea	110 (23.31%)	24 (10.08%)
Epistaxis	156 (33.05%)	43 (18.07%)
Oropharyngeal pain	74 (15.68%)	31 (13.03%)
Pneumonitis	66 (13.98%)	11 (4.62%)
Productive cough	25 (5.30%)	14 (5.88%)
Rhinorrhoea	43 (9.11%)	18 (7.56%)
Skin and subcutaneous tissue disorders		
Acne	29 (6.14%)	4 (1.68%)
Alopecia	221 (46.82%)	125 (52.52%)

Dry skin	37 (7.84%)	20 (8.40%)
Erythema	49 (10.38%)	16 (6.72%)
Nail disorder	68 (14.41%)	27 (11.34%)
Pruritus	64 (13.56%)	24 (10.08%)
Rash	191 (40.47%)	49 (20.59%)
Vascular disorders		
Hot flush	13 (2.75%)	12 (5.04%)
Hypertension	74 (15.68%)	27 (11.34%)

Other Relevant Findings

N/A

Conclusion:

The results of this exploratory analysis showed no OS benefit with everolimus treatment in the full population. However, in the HR-negative subpopulation, treatment with everolimus was associated with a longer OS, consistent with the PFS benefit, as previously shown.
The overall safety profile of everolimus in combination with trastuzumab and paclitaxel remains consistent with that reported in the previous CSRs. The safety profile was generally consistent with the known everolimus safety profile.

Date of Clinical Trial Report

Progression Free Survival (PFS) CSR: 27 April 2015
Overall Survival (OS) CSR: 16 Sep 2016
Final Close Out CSR: 24 July 2018