Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Everolimus

Trial Indication(s)

HER2/neu over-expressing locally advanced or metastatic breast cancer

Protocol Number

CRAD001W2301

Protocol Title

A randomized Phase III, double-blind, placebo-controlled multicenter trial of daily everolimus in combination with trastuzumab and vinorelbine, in pretreated women with HER2/neu over-expressing locally advanced or metastatic breast cancer.

Clinical Trial Phase

Phase 3

Phase of Drug Development

III

Study Start/End Dates

Study Start Date: October 2009 (Actual)
Study Completion Date: June 2015 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

The study employed a 2-look group-sequential design for the evaluation of the primary efficacy endpoint of PFS (assessed as per local Investigator assessment). Survival function of PFS or OS for each treatment arm was estimated using Kaplan-Meier methodology. The primary efficacy analysis was the comparison of PFS between treatment arms using a stratified log-rank test at anoverall one-sided 2.5% level of significance (strata information on prior lapatinib use was based on the randomization stratification factors obtained through IXRS). The hazard ratio (HR) of the PFS, along with its two-sided 95% confidence interval (CI), was estimated using a stratified Cox proportional hazards model.

Centers

199 centers in 21 countries: United States(66), Turkey(4), Thailand(4), Slovakia (Slovak Republic)(2), Singapore(1), Poland(4), Mexico(3), Japan(13), Italy(6), Israel(5), Hungary(4), Greece(6), United Kingdom(8), France(8), Spain(18), Germany(14), Czech Republic(4), China(6), Belgium(6), Australia(7), Argentina(10)

Objectives:

The primary objective of this study is to compare the combination of everolimus, vinorelbine and trastuzumab to the combination of vinorelbine and trastuzumab with respect to progression-free survival, based on local radiological review, in women with HER2/neu overexpressing advanced or metastatic breast cancer who are resistant to trastuzumab and have been pre-treated with a taxane.

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

Oral everolimus (5 mg/day) or matching placebo + intravenous vinorelbine (25 mg/m2 weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)

Statistical Methods

The study employed a 2-look group-sequential design for the evaluation of the primary efficacy endpoint of PFS (assessed as per local Investigator assessment). A total of 417 PFS events were targeted. The study design incorporated a pre-planned interim analysis after observing 251 (60%) of the required PFS events. The primary efficacy analysis was the comparison of PFS between treatment arms using a stratified log-rank test at an overall one-sided 2.5% level of significance (strata information on prior lapatinib use was based on the randomization stratification factors obtained through IXRS). The survival distribution function of PFS was estimated using Kaplan-Meier method. The hazard ratio (HR) of the PFS, along with its two-sided 95% confidence interval (CI), was estimated using a stratified Cox proportional hazards model.
Survival function of OS was estimated using Kaplan-Meier methodology. The two treatment groups were compared using a stratified log-rank test at an overall one-sided 2.5% level of significance. A stratified Cox regression was used to estimate the HR for OS and its 95% CI.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
• Histologically or cytologically confirmed invasive breast carcinoma with locally recurrent or radiological evidence of metastatic disease. Locally recurrent disease must not be amenable to resection with curative intent.
• HER2+ status defined as IHC 3+ staining or in situ hybridization positive
• Patients with resistance to trastuzumab
• Prior taxane therapy
• Patients with an ECOG performance status of 0 - 2
• Patients with measurable disease as per RECIST criteria
• Documentation of negative pregnancy test for patients of child bearing potential prior to enrollment within 7 days prior to randomization. Sexually active pre-menopausal women must use adequate contraceptive measures, excluding estrogen containing contraceptives, while on study;
• Patients must meet laboratory criteria defined in the study within 21 days prior to randomization

Exclusion Criteria:
• Prior mTOR inhibitors or vinca alkaloid agents for the treatment of cancer
• More than three prior chemotherapy lines for advanced disease.
• Symptomatic CNS metastases or evidence of leptomeningeal disease. Previously treated asymptomatic CNS metastases are allowed provided that the last treatment for CNS metastases was completed >8 weeks prior to randomization
• Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral everolimus
• Peripheral neuropathy ≥ grade 2 at randomization
• Active cardiac disease
• History of cardiac dysfunction
• Any malignancy within 5 years prior to randomization, with the exception of adequately treated in-situ carcinoma of the cervix uteri, basal or squamous cell carcinoma or non-melanomatous skin cancer
• Known hypersensitivity to any study medication
• Breastfeeding or pregnant

Participant Flow Table

Overall Study

	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab
Started	280	282
Patients Untreated	4[1]	3[1]
Completed	3[2]	7[2]
Not Completed	277[2]	275[2]
Adverse Event	29	14
Abnormal test procedure	0	1
Disease progression	217	242

New cancer therapy	5	1
Protocol Violation	1	1
Withdrawal by Subject	19	14
Lost to Follow-up	1	0
Administrative problems	2	0
Death	3	2

[1] Untreated = randomized but did not receive study treatment
[2] Pts completed= on treatment at time of DCO. Not Completed = ended treatment as per protocol.

Baseline Characteristics

	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab	Total
Number of Participants [units: participants]	284	285	569
Age Continuous (units: years) Mean ± Standard Deviation	54.3±10.98	53.4±11.00	53.8±10.99
Gender, Male/Female (units: Participants)			
Female	284	285	569
Male	0	0	0

Summary of Efficacy

Primary Outcome Result(s)

Progressive-free survival (PFS) per Investigator assessment

	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab
Number of Participants Analyzed [units: participants]	284	285
Progressive-free survival (PFS) per Investigator assessment (units: months) Median (95% Confidence Interval)	7.00 (6.74 to 8.18)	5.78 (5.49 to 6.90)

Statistical Analysis

Groups	Everolimus + vinorelbine + trastuzumab, placebo + vinorelbine + trastuzumab
Non-Inferiority/Equivalence Test	No
P Value	0.0067
Method	Log Rank
Hazard Ratio (HR)	0.78
95 % Confidence Interval 2-Sided	0.65 to 0.95

Secondary Outcome Result(s)

Overall survival (OS)

	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab
Number of Participants Analyzed [units: participants]	284	285
Overall survival (OS) (units: months) Median (95% Confidence Interval)	23.46 (20.01 to 28.81)	24.08 (21.49 to 27.63)

Overall response rate (ORR)

	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab
Number of Participants Analyzed [units: participants]	284	285
Overall response rate (ORR) (units: Percentage of participants) Number (95% Confidence Interval)	40.8 (35.1 to 46.8)	37.2 (31.6 to 43.1)

Clinical benefit rate (CBR)

	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab
Number of Participants Analyzed [units: participants]	284	285
Clinical benefit rate (CBR) (units: Percentage of participants) Number (95% Confidence Interval)	59.2 (53.2 to 64.9)	53.3 (47.4 to 59.2)

Time to deterioration of the ECOG performance status score

	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab
Number of Participants Analyzed [units: participants]	284	285
Time to deterioration of the ECOG performance status score (units: months)	32.66	21.55

PRO: Time to deterioration in global health status/QoL domain score of the European Organization for the Research and Treatment of Cancer (EORTC)–Core Quality of Life Questionnaire (QLQ-C30) (by at least 10%)

	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab
Number of Participants Analyzed [units: participants]	284	285

PRO: Time to deterioration in global health status/QoL domain score of the European Organization for the Research and Treatment of Cancer (EORTC)–Core Quality of Life Questionnaire (QLQ-C30) (by at least 10%) (units: months) Median (95% Confidence Interval)		
Deterioration - global QoL domain by at least 10%	8.31 (6.93 to 11.53)	7.29 (5.55 to 10.38)
Deterioration in the PF domain by at least 10%	11.96 (8.31 to 14.09)	12.48 (8.31 to 20.86)
Deterioration in the EF domain by at least 10%	15.18 (9.20 to 17.28)	12.45 (9.69 to 16.36)
Deterioration in the SF domain by at least 10%	11.33 (8.18 to 14.52)	13.11 (8.31 to 19.32)

Everolimus blood concentrations by leading dose and time point

	Everolimus 2.5 mg	**Everolimus**
Number of Participants Analyzed [units: participants]	10	43
Everolimus blood concentrations by leading dose and time point (units: ng/ml) Mean ± Standard Deviation		
Pre-dose (Cmin) (n: 7, 32)	2.928 ± 2.6197	5.652 ± 4.1006
2 hours post administration (C2h) (n:10, 43)	13.035 ± 6.6842	22.005 ± 13.3800

Vinorelbine blood concentrations by leading dose and time point

	Everolimus	Everolimus Placebo
Number of Participants Analyzed [units: participants]	76	64
Vinorelbine blood concentrations by leading dose and time point (units: ng/ml) Mean ± Standard Deviation		
Pre-infusion - dose (Cmin) (n: 76, 64)	11.085 ± 66.8551	0.061 ± 0.4888
End of infusion (Cmax) (n: 58, 49)	867.147 ± 971.3057	1068.51 ± 1145.860

Trastuzumab blood concentrations by leading dose and time point

	Everolimus	Everolimus Placebo
Number of Participants Analyzed [units: participants]	74	59
Trastuzumab blood concentrations by leading dose and time point (units: ng/ml) Mean ± Standard Deviation		
Pre-infusion - dose (Cmin) (n: 73, 57)	23.351 ± 6.3344	24.526 ± 7.9960
End of infusion (Cmax) (n: 75, 59)	64.279 ± 27.8549	60.576 ± 15.5198

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

	Everolimus + Trastuzumab + Vinorelbine N = 280	Placebo + Trastuzumab + Vinorelbine N = 282
Total participants affected	122 (43.57%)	58 (20.57%)
Blood and lymphatic system disorders		
Agranulocytosis[1, †]	0 (0.00%)	1 (0.35%)
Anaemia[1, †]	10 (3.57%)	2 (0.71%)
Febrile neutropenia[1, †]	30 (10.71%)	4 (1.42%)
Immune thrombocytopenic purpura[1, †]	1 (0.36%)	0 (0.00%)
Leukopenia[1, †]	3 (1.07%)	0 (0.00%)
Neutropenia[1, †]	12 (4.29%)	3 (1.06%)
Thrombocytopenia[1, †]	4 (1.43%)	1 (0.35%)
Cardiac disorders		
Acute myocardial infarction[1, †]	1 (0.36%)	0 (0.00%)
Cardiac failure[1, †]	1 (0.36%)	0 (0.00%)
Eye disorders		
Cataract[1, †]	2 (0.71%)	1 (0.35%)

Cataract subcapsular[1, †]	0 (0.00%)	1 (0.35%)
Vision blurred[1, †]	1 (0.36%)	0 (0.00%)
Gastrointestinal disorders		
Abdominal pain[1, †]	1 (0.36%)	1 (0.35%)
Abdominal pain upper[1, †]	2 (0.71%)	1 (0.35%)
Ascites[1, †]	1 (0.36%)	0 (0.00%)
Constipation[1, †]	1 (0.36%)	0 (0.00%)
Diarrhoea[1, †]	5 (1.79%)	2 (0.71%)
Dysphagia[1, †]	1 (0.36%)	0 (0.00%)
Gastric perforation[1, †]	0 (0.00%)	1 (0.35%)
Gastritis[1, †]	2 (0.71%)	0 (0.00%)
Gastrointestinal inflammation[1, †]	0 (0.00%)	1 (0.35%)
Haematemesis[1, †]	0 (0.00%)	1 (0.35%)
Haematochezia[1, †]	1 (0.36%)	0 (0.00%)
Ileus[1, †]	1 (0.36%)	0 (0.00%)
Intestinal obstruction[1, †]	1 (0.36%)	0 (0.00%)
Nausea[1, †]	3 (1.07%)	1 (0.35%)
Neutropenic colitis[1, †]	1 (0.36%)	0 (0.00%)
Pancreatitis[1, †]	0 (0.00%)	1 (0.35%)
Stomatitis[1, †]	9 (3.21%)	1 (0.35%)
Vomiting[1, †]	5 (1.79%)	2 (0.71%)
General disorders and administration site conditions		
Asthenia[1, †]	0 (0.00%)	1 (0.35%)
Chills[1, †]	2 (0.71%)	0 (0.00%)

Device dislocation[1, †]	0 (0.00%)	1 (0.35%)
Extravasation[1, †]	1 (0.36%)	0 (0.00%)
General physical health deterioration[1, †]	3 (1.07%)	2 (0.71%)
Hyperpyrexia[1, †]	0 (0.00%)	1 (0.35%)
Hyperthermia[1, †]	0 (0.00%)	1 (0.35%)
Inflammation[1, †]	0 (0.00%)	1 (0.35%)
Non-cardiac chest pain[1, †]	2 (0.71%)	0 (0.00%)
Pyrexia[1, †]	13 (4.64%)	5 (1.77%)
Systemic inflammatory response syndrome[1, †]	1 (0.36%)	0 (0.00%)
Hepatobiliary disorders		
Bile duct obstruction[1, †]	0 (0.00%)	2 (0.71%)
Cholecystitis[1, †]	1 (0.36%)	0 (0.00%)
Hepatic mass[1, †]	0 (0.00%)	1 (0.35%)
Hepatocellular injury[1, †]	1 (0.36%)	0 (0.00%)
Infections and infestations		
Abscess jaw[1, †]	0 (0.00%)	1 (0.35%)
Aspergillus infection[1, †]	1 (0.36%)	0 (0.00%)
Bronchiolitis[1, †]	0 (0.00%)	1 (0.35%)
Bronchitis[1, †]	0 (0.00%)	1 (0.35%)
Cellulitis[1, †]	4 (1.43%)	0 (0.00%)
Clostridium difficile colitis[1, †]	1 (0.36%)	0 (0.00%)
Conjunctivitis[1, †]	1 (0.36%)	0 (0.00%)

Device related infection[1, †]	3 (1.07%)	1 (0.35%)
Device related sepsis[1, †]	1 (0.36%)	0 (0.00%)
Escherichia sepsis[1, †]	1 (0.36%)	0 (0.00%)
Escherichia urinary tract infection[1, †]	1 (0.36%)	0 (0.00%)
Furuncle[1, †]	1 (0.36%)	0 (0.00%)
Gastroenteritis[1, †]	2 (0.71%)	0 (0.00%)
Gastroenteritis clostridial[1, †]	1 (0.36%)	0 (0.00%)
Herpes zoster[1, †]	1 (0.36%)	1 (0.35%)
Influenza[1, †]	2 (0.71%)	0 (0.00%)
Klebsiella bacteraemia[1, †]	1 (0.36%)	0 (0.00%)
Lobar pneumonia[1, †]	1 (0.36%)	0 (0.00%)
Lung infection[1, †]	2 (0.71%)	0 (0.00%)
Neutropenic infection[1, †]	1 (0.36%)	0 (0.00%)
Neutropenic sepsis[1, †]	2 (0.71%)	0 (0.00%)
Osteomyelitis[1, †]	1 (0.36%)	0 (0.00%)
Parainfluenzae virus infection[1, †]	1 (0.36%)	0 (0.00%)
Peritonitis[1, †]	1 (0.36%)	0 (0.00%)
Peritonsillar abscess[1, †]	1 (0.36%)	0 (0.00%)
Pharyngitis[1, †]	2 (0.71%)	0 (0.00%)
Pneumocystis jirovecii infection[1, †]	0 (0.00%)	1 (0.35%)
Pneumonia[1, †]	8 (2.86%)	1 (0.35%)
Postoperative wound infection[1, †]	1 (0.36%)	0 (0.00%)

Pseudomonal sepsis[1, †]	0 (0.00%)	1 (0.35%)
Sepsis[1, †]	3 (1.07%)	0 (0.00%)
Sinusitis[1, †]	0 (0.00%)	1 (0.35%)
Soft tissue infection[1, †]	1 (0.36%)	0 (0.00%)
Tuberculosis[1, †]	1 (0.36%)	0 (0.00%)
Upper respiratory tract infection[1, †]	0 (0.00%)	1 (0.35%)
Urinary tract infection[1, †]	1 (0.36%)	2 (0.71%)
Viral upper respiratory tract infection[1, †]	0 (0.00%)	1 (0.35%)
Injury, poisoning and procedural complications		
Fall[1, †]	1 (0.36%)	0 (0.00%)
Femur fracture[1, †]	1 (0.36%)	1 (0.35%)
Fractured sacrum[1, †]	0 (0.00%)	1 (0.35%)
Hand fracture[1, †]	0 (0.00%)	1 (0.35%)
Humerus fracture[1, †]	2 (0.71%)	0 (0.00%)
Pelvic fracture[1, †]	0 (0.00%)	1 (0.35%)
Procedural pain[1, †]	0 (0.00%)	1 (0.35%)
Spinal compression fracture[1, †]	0 (0.00%)	1 (0.35%)
Subdural haematoma[1, †]	1 (0.36%)	0 (0.00%)
Thoracic vertebral fracture[1, †]	0 (0.00%)	1 (0.35%)
Wound dehiscence[1, †]	1 (0.36%)	0 (0.00%)
Investigations		
Neutrophil count	1 (0.36%)	0 (0.00%)

decreased[1, †]		
Metabolism and nutrition disorders		
Cachexia[1, †]	1 (0.36%)	0 (0.00%)
Decreased appetite[1, †]	1 (0.36%)	1 (0.35%)
Dehydration[1, †]	1 (0.36%)	0 (0.00%)
Diabetes mellitus[1, †]	2 (0.71%)	1 (0.35%)
Hyperglycaemia[1, †]	1 (0.36%)	0 (0.00%)
Hyperkalaemia[1, †]	0 (0.00%)	1 (0.35%)
Hypocalcaemia[1, †]	1 (0.36%)	0 (0.00%)
Hypokalaemia[1, †]	1 (0.36%)	0 (0.00%)
Hyponatraemia[1, †]	2 (0.71%)	1 (0.35%)
Type 2 diabetes mellitus[1, †]	1 (0.36%)	0 (0.00%)
Musculoskeletal and connective tissue disorders		
Bone pain[1, †]	2 (0.71%)	0 (0.00%)
Flank pain[1, †]	1 (0.36%)	0 (0.00%)
Musculoskeletal pain[1, †]	0 (0.00%)	1 (0.35%)
Neck pain[1, †]	0 (0.00%)	1 (0.35%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Metastases to central nervous system[1, †]	1 (0.36%)	1 (0.35%)
Paraneoplastic syndrome[1, †]	1 (0.36%)	0 (0.00%)
Thyroid cancer[1, †]	1 (0.36%)	0 (0.00%)

Nervous system disorders		
Brain oedema[1, †]	1 (0.36%)	1 (0.35%)
Disturbance in attention[1, †]	1 (0.36%)	0 (0.00%)
Dizziness[1, †]	0 (0.00%)	1 (0.35%)
Headache[1, †]	2 (0.71%)	3 (1.06%)
Hydrocephalus[1, †]	1 (0.36%)	0 (0.00%)
Migraine[1, †]	1 (0.36%)	0 (0.00%)
Neuralgia[1, †]	1 (0.36%)	0 (0.00%)
Neurological symptom[1, †]	0 (0.00%)	1 (0.35%)
Neuropathy peripheral[1, †]	1 (0.36%)	0 (0.00%)
Seizure[1, †]	3 (1.07%)	1 (0.35%)
Somnolence[1, †]	0 (0.00%)	1 (0.35%)
Syncope[1, †]	1 (0.36%)	0 (0.00%)
Psychiatric disorders		
Suicide attempt[1, †]	0 (0.00%)	1 (0.35%)
Renal and urinary disorders		
Acute kidney injury[1, †]	3 (1.07%)	0 (0.00%)
Dysuria[1, †]	1 (0.36%)	0 (0.00%)
Reproductive system and breast disorders		
Breast pain[1, †]	1 (0.36%)	0 (0.00%)
Ovarian cyst[1, †]	1 (0.36%)	1 (0.35%)
Pelvic pain[1, †]	1 (0.36%)	0 (0.00%)
Uterine haemorrhage[1, †]	1 (0.36%)	0 (0.00%)

Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome[1, †]	1 (0.36%)	0 (0.00%)
Cough[1, †]	1 (0.36%)	2 (0.71%)
Dyspnoea[1, †]	3 (1.07%)	3 (1.06%)
Dyspnoea exertional[1, †]	0 (0.00%)	1 (0.35%)
Epistaxis[1, †]	3 (1.07%)	0 (0.00%)
Haemothorax[1, †]	0 (0.00%)	1 (0.35%)
Hypoxia[1, †]	1 (0.36%)	1 (0.35%)
Interstitial lung disease[1, †]	3 (1.07%)	0 (0.00%)
Oropharyngeal pain[1, †]	0 (0.00%)	1 (0.35%)
Pleural effusion[1, †]	1 (0.36%)	5 (1.77%)
Pneumonitis[1, †]	2 (0.71%)	3 (1.06%)
Pneumothorax[1, †]	0 (0.00%)	1 (0.35%)
Pulmonary arterial hypertension[1, †]	0 (0.00%)	1 (0.35%)
Pulmonary embolism[1, †]	3 (1.07%)	5 (1.77%)
Respiratory failure[1, †]	0 (0.00%)	3 (1.06%)
Tachypnoea[1, †]	0 (0.00%)	1 (0.35%)
Skin and subcutaneous tissue disorders		
Rash[1, †]	1 (0.36%)	0 (0.00%)
Skin ulcer[1, †]	1 (0.36%)	0 (0.00%)
Vascular disorders		
Deep vein thrombosis[1, †]	1 (0.36%)	0 (0.00%)

Haematoma[1, †]	0 (0.00%)	1 (0.35%)
Haemorrhage[1, †]	0 (0.00%)	1 (0.35%)
Hypotension[1, †]	1 (0.36%)	2 (0.71%)
Shock[1, †]	0 (0.00%)	1 (0.35%)
Thrombosis[1, †]	0 (0.00%)	1 (0.35%)

† Systematic Assessment
1 MedDRA V18.0

Other Adverse Events by System Organ Class

Frequent Event Reporting Threshold 5%

	Everolimus + Trastuzumab + Vinorelbine N = 280	Placebo + Trastuzumab + Vinorelbine N = 282
Total participants affected	280 (100.00%)	280 (99.29%)
Blood and lymphatic system disorders		
Anaemia[1, †]	137 (48.93%)	85 (30.14%)
Febrile neutropenia[1, †]	17 (6.07%)	7 (2.48%)
Leukopenia[1, †]	126 (45.00%)	105 (37.23%)
Neutropenia[1, †]	226 (80.71%)	196 (69.50%)
Thrombocytopenia[1, †]	39 (13.93%)	6 (2.13%)
Gastrointestinal disorders		
Abdominal pain[1, †]	45 (16.07%)	52 (18.44%)

Abdominal pain upper[1, †]	34 (12.14%)	40 (14.18%)
Constipation[1, †]	84 (30.00%)	88 (31.21%)
Diarrhoea[1, †]	108 (38.57%)	88 (31.21%)
Dry mouth[1, †]	14 (5.00%)	7 (2.48%)
Dyspepsia[1, †]	21 (7.50%)	25 (8.87%)
Mouth ulceration[1, †]	32 (11.43%)	6 (2.13%)
Nausea[1, †]	98 (35.00%)	105 (37.23%)
Stomatitis[1, †]	174 (62.14%)	78 (27.66%)
Vomiting[1, †]	57 (20.36%)	59 (20.92%)
General disorders and administration site conditions		
Asthenia[1, †]	74 (26.43%)	57 (20.21%)
Chills[1, †]	18 (6.43%)	18 (6.38%)
Fatigue[1, †]	124 (44.29%)	119 (42.20%)
Non-cardiac chest pain[1, †]	11 (3.93%)	20 (7.09%)
Oedema peripheral[1, †]	39 (13.93%)	23 (8.16%)
Pain[1, †]	20 (7.14%)	20 (7.09%)
Pyrexia[1, †]	107 (38.21%)	65 (23.05%)
Infections and infestations		
Nasopharyngitis[1, †]	37 (13.21%)	29 (10.28%)
Upper respiratory tract infection[1, †]	38 (13.57%)	26 (9.22%)
Urinary tract infection[1, †]	26 (9.29%)	18 (6.38%)
Investigations		

Alanine aminotransferase increased[1, †]	37 (13.21%)	26 (9.22%)
Aspartate aminotransferase increased[1, †]	33 (11.79%)	22 (7.80%)
Ejection fraction decreased[1, †]	17 (6.07%)	5 (1.77%)
Gamma-glutamyltransferase increased[1, †]	29 (10.36%)	23 (8.16%)
Haemoglobin decreased[1, †]	22 (7.86%)	18 (6.38%)
Neutrophil count decreased[1, †]	14 (5.00%)	8 (2.84%)
Weight decreased[1, †]	83 (29.64%)	47 (16.67%)
White blood cell count decreased[1, †]	17 (6.07%)	23 (8.16%)
Metabolism and nutrition disorders		
Decreased appetite[1, †]	94 (33.57%)	49 (17.38%)
Hypercholesterolaemia[1, †]	26 (9.29%)	12 (4.26%)
Hyperglycaemia[1, †]	26 (9.29%)	15 (5.32%)
Hypertriglyceridaemia[1, †]	23 (8.21%)	9 (3.19%)
Hypokalaemia[1, †]	34 (12.14%)	19 (6.74%)
Musculoskeletal and connective tissue disorders		
Arthralgia[1, †]	48 (17.14%)	36 (12.77%)
Back pain[1, †]	37 (13.21%)	46 (16.31%)

Bone pain[1, †]	28 (10.00%)	24 (8.51%)
Muscle spasms[1, †]	31 (11.07%)	47 (16.67%)
Musculoskeletal chest pain[1, †]	16 (5.71%)	12 (4.26%)
Musculoskeletal pain[1, †]	14 (5.00%)	14 (4.96%)
Myalgia[1, †]	39 (13.93%)	31 (10.99%)
Pain in extremity[1, †]	42 (15.00%)	44 (15.60%)
Nervous system disorders		
Dizziness[1, †]	31 (11.07%)	24 (8.51%)
Dysgeusia[1, †]	32 (11.43%)	17 (6.03%)
Headache[1, †]	74 (26.43%)	62 (21.99%)
Hypoaesthesia[1, †]	15 (5.36%)	7 (2.48%)
Neuropathy peripheral[1, †]	27 (9.64%)	41 (14.54%)
Paraesthesia[1, †]	21 (7.50%)	21 (7.45%)
Peripheral sensory neuropathy[1, †]	25 (8.93%)	17 (6.03%)
Psychiatric disorders		
Anxiety[1, †]	13 (4.64%)	18 (6.38%)
Insomnia[1, †]	34 (12.14%)	27 (9.57%)
Respiratory, thoracic and mediastinal disorders		
Cough[1, †]	84 (30.00%)	55 (19.50%)
Dyspnoea[1, †]	51 (18.21%)	40 (14.18%)
Epistaxis[1, †]	64 (22.86%)	38 (13.48%)
Oropharyngeal pain[1, †]	27 (9.64%)	27 (9.57%)

Pneumonitis[1, †]	17 (6.07%)	9 (3.19%)
Rhinorrhoea[1, †]	17 (6.07%)	14 (4.96%)
Skin and subcutaneous tissue disorders		
Alopecia[1, †]	22 (7.86%)	29 (10.28%)
Pruritus[1, †]	16 (5.71%)	29 (10.28%)
Rash[1, †]	71 (25.36%)	54 (19.15%)
Vascular disorders		
Hot flush[1, †]	4 (1.43%)	16 (5.67%)
Hypertension[1, †]	24 (8.57%)	10 (3.55%)
Phlebitis[1, †]	14 (5.00%)	18 (6.38%)

† Systematic Assessment
1 MedDRA V18.0

Other Relevant Findings

None

Conclusion:

Results demonstrate clinically important treatment benefit of everolimus + trastuzumab + vinorelbine compared to treatment with trastuzumab + vinorelbine alone in women with HER2+ advanced or metastatic breast cancer who are resistant to trastuzumab and have been pre-treated with a taxane.

- The primary endpoint was met, showing a 22% reduction in risk in PFS. Results of the secondary efficacy endpoints were also supportive of the primary variable. Interim OS data, though immature, the median OS is numerically higher in the everolimus arm (by approximately 4 months) than in the placebo arm.
- The safety and tolerability profile of everolimus is consistent to that previously seen in the oncology setting and the PRO data were similar for both treatment arms indicating that the cytopenia-related incremental toxicity did not have a negative impact on ECOG PS or QoL.

In conclusion, the magnitude of the PFS effect together with the positively trending OS seen in this heavily pre-treated patient population can be considered a net clinical benefit and might represent an important improvement in the management of this heavily pre-treated patient population with HER2+ advanced or metastatic breast cancer.

Date of Clinical Trial Report

1-Dec-2015