Sponsor

Novartis

Generic Drug Name

Rad001 (everolimus)

Therapeutic Area of Trial

Primary breast cancer in postmenopausal women.

Approved Indication

Everolimus is approved in several countries, including the USA, for use as prophylaxis in combination with cyclosporine A and glucocorticoids to prevent renal and cardiac transplant rejection. In oncology, it has also been approved for use as a cancer treatment of renal cell carcinomas (RCC), pancreatic neuroendocrine tumors (pNET), and subependemal giant cell astrocytomas (SEGA).

Study Number

CRAD001C2222

Title

A phase II, double-blind, randomized, placebo-controlled, multicenter study assessing the value of adding RAD001 to letrozole (Femara®) as preoperative therapy of primary breast cancer in postmenopausal women.

Phase of Development

Phase II

Study Start/End Dates

22-Mar-2005 to 04-Apr-2007

Study Design/Methodology

This was a phase II study with two stages.

Stage I was a double-blind, placebo controlled, multicenter stage that randomized patients into two treatment arms: 1) everolimus 10 mg + letrozole 2.5 mg or 2) letrozole 2.5 mg + placebo. Both treatment regimens were administered daily for 4 months prior to undergoing breast-conserving surgery or mastectomy.

Stage II was planned as an open-label study expansion that would enroll all patients into one treatment arm where they received a daily dose of everolimus 10 mg + letrozole 2.5 mg continuously for 4 months prior to undergoing breast conserving surgery or mastectomy. Surgery was

scheduled 16 weeks from the date the first treatment was received. Patients received their last study treatment ≤ 24 hours before surgery. An interim analysis was scheduled before enrolling patients into Stage II to assess the efficacy and safety of treatment in Stage I.

The Stage I analysis results formed the basis for the Study Steering Committee (SSC) recommendation on Stage 2. The SSC recommended that Stage II should not go ahead.

Centres

Thirty eight centers in 10 countries: Austria (4), Belgium (1), Canada (1), France (4), Germany (7), Italy (4), Russia (4), Spain (6), United Kingdom (3), United States (4).

Publication

Baselga J, Semiglazov V, van Dam P, et al (2007) Phase II double-blind randomized trial of daily oral RAD001 (everolimus) plus letrozole (LET) or placebo (P) plus LET as neoadjuvant therapy for ER+ breast cancer. Breast Cancer Research and Treatment; 106(S1):S107, Abstract 2066

Objectives

Primary objectives

- Assess the added efficacy obtained by the association of everolimus with letrozole as peroperative therapy of primary, HR+ breast cancer in postmenopausal women as shown by increased clinical tumot response rates.Identify a subgroup of patients that is most likely to benefit from the combination of everolimus + letrozole as defined by their pretreatment molecular tumor characteristics.

Secondary objectives

- Compare safety and tolerability of the treatment regimens.
- Investigate whether a reduction in tumor volume was correlated to changes in biological marker expression.
- Compare between groups the number of patients undergoing breast-conserving surgery rather than mastectomy after 4 months of treatment.
- Compare the frequency of complete pathological response (pCR) in the two arms after 4 months of treatment.
- Investigate whether co-administration of everolimus 10 mg/day with letrozole 2.5 mg/day influences letrozole pharmacokinetics and whether exposure to everolimus is altered in the presence of letrozole compared with historical exposure data.
- Investigate tumor-specific mutations and compare gene expression changes in tumor cells for biomarker development.
- Investigate whether individual genetic characteristics predict response to treatment, susceptibility to adverse events (AEs), or drug-drug interactions.

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

Oral tablets of everolimus 10 mg and letrozole 2.5 mg once daily.

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

Oral tablets of everolimus matching placebo and letrozole 2.5 mg once daily.

Criteria for Evaluation

Primary variables

- The primary efficacy variable was the calculated overall response rate (complete response [CR] + partial response [PR]) based on the clinical palpation assessment after 4 months of treatment.
- Molecular marker analysis using tumor biopsy samples was also primary for the study. Immunohistochemistry (IHC) tests, fluorescence in situ hybridization (FISH) and deoxyribonucleic acid (DNA) analyses were performed.

Secondary variables

- Secondary efficacy variables were response rates (CR + PR) at 4 months evaluated by mammography and ultrasound.

Safety and tolerability

Safety and tolerability was assessed according to the NIH/NCI CTCAE version 3.

- Assessed by collecting all AEs, serious AEs (SAEs), with their severity and relationship to study drug, and pregnancies. It included regular monitoring of hematology, blood chemistry, and urine performed at the central laboratory and regular assessments of vital signs, ECG, physical condition, and body weight.

Pharmacology

- Trough drug levels for everolimus and letrozole were measured after 15 or 28 days of treatment and prior to surgery at study end for all patients.

Other

- Optional biomarker and pharmacogenetics studies were conducted using tumor and blood samples from consenting patients.

Statistical Methods

Efficacy

The overall tumor response was calculated using the measurements of breast tumor and the assessment of axillary lymph nodes recorded by the investigator. Response rate at four months was estimated by the change from baseline to last clinical tumor assessment performed and was calculated and categorized based on the modified WHO criteria.

The calculated overall response rate and 95% confidence intervals were presented by treatment arm. This primary endpoint was compared between the two treatment arms by a Chi-square test (significance threshold: 1-sided p value ≤ 0.10). The percentage rates of CR, PR, NC and PD at 4 months based on clinical palpation were also presented for each treatment arm.

As supportive analysis, a logistic regression analysis was performed using this primary endpoint as response and as explanatory variables: Baseline, HER2+ (Yes, No), tumor size (≤5 cm, >5 cm), nodal involvement (Yes, No) and planned type of surgery (Breast Conserving Surgery, Mastectomy). As HER2+ status was not available for all patients this analysis was also repeated without the inclusion of this variable.

Secondary efficacy analyses consisted of response rates at 4 months evaluated by mammography and ultrasound. The change from baseline to last available assessment was calculated and categorized according to the modified WHO criteria. These breast tumor response rates are tabulated by treatment arm and analyzed using a Chi-square test (significance threshold: 1-sided p value ≤0.10).

The biomarkers nominated as candidate markers for the search for a possible subpopulation were pAKT, pS6 240, Ki-67, Cyclin D, HER2, PI3K, PTEN and Body Mass Index (BMI). The continuous markers pAKT, pS6 240, Ki-67, Cyclin D and BMI were dichotomized using predetermined cut-off values based on the HScore or % staining and were defined based on a group review of graphical presentations of all of the baseline biopsy sample data prior to database lock.

Safety

The assessment of safety is based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs, special tests) are considered as appropriate. All safety outputs use the safety population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Female patients ≥ 18 years old with a histologically confirmed diagnosis of invasive breast cancer, previously untreated (patients who had been treated for cancer of the contralateral breast could have been included if there was at least a 2-year time interval from last systemic treatment for breast cancer before randomization into this study).
- Candidates for mastectomy or breast-conserving surgery.
- Primary tumor palpable and > 2 cm in diameter, as measured by imaging.
- Primary tumor is ER+, defined as: ≥ 10% of the nuclei in the invasive component of the tumor stain positive after immunostaining (analyzed in local laboratory).
- Clinical stage M0 (bone scan, chest x-ray, and abdominal computed tomography (CT) scan or liver ultrasound required at screening to exclude metastatic disease).
- Postmenopausal as defined by any of the following criteria:
  - Radiation-induced menopause or surgical bilateral oophorectomy
  - Women with an intact uterus and
    - ≥ 55 years of age, or
    - < 55 years of age without menses for the last 5 years, or
    - < 55 years of age without menses for at least the last 12 months (but with menses in

the last 5 years) and has postmenopausal levels of follicle stimulating hormone (FSH) (according to the postmenopausal range of the individual laboratory and performed at least four weeks after stopping hormone replacement therapy/oral contraceptives)

- Women without an intact uterus and
  - ≥ 55 years of age, or
  - < 55 years of age and postmenopausal levels of FSH (according to the postmenopausal range of the individual laboratory, and performed at least four weeks after stopping hormone replacement therapy/oral contraceptives

- WHO performance status ≤ 1
- Adequate bone marrow function as shown by white blood cell (WBC) count ≥ 3.5 x 10^9/L, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelets ≥ lower limit of normal (LLN), hemoglobin > 10 g/dL
- Adequate liver function as shown by serum bilirubin ≤ 1.5 x upper limit of the normal range (ULN), albumin ≥ 3 g/dL, serum transaminases activity (ALT and AST)
- ≤ 2.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN
- Normal renal function as shown by serum creatinine ≤ 1.5 x ULN and blood urea nitrogen (BUN) ≤ 1.5 x ULN
- Provided written informed consent

Exclusion Criteria

- Multicentric invasive tumors (defined as additional foci of tumor outside the breast quadrant containing the primary tumor)
- Bilateral or inflammatory breast cancer (a bilateral mammography was required at screening visit)
- Receipt of concomitant anti-cancer treatments such as chemotherapy, immunotherapy/biological response modifiers, endocrine therapy (including steroids), and radiotherapy. Patients who had received hormone replacement therapy were **not** excluded, provided that such therapy was discontinued at least 2 weeks prior to screening assessments.
- Known hypersensitivity to everolimus or sirolimus (rapamycin), letrozole, or lactose (contained in formulations of everolimus and letrozole)
- Grade ≥ 3 hypercholesterolemia/hypertriglyceridemia or grade ≥ 2 hypercholesterolemia/ hypertriglyceridemia with history of coronary artery disease (despite lipid-lowering treatment if given)
- Uncontrolled infection or other concurrent severe and/or uncontrolled medical disease that could compromise participation in the study, including:
  - Uncontrolled diabetes mellitus (fasting serum glucose > 120 mg/dL, 6.7 mmol/L).
  - Uncontrolled cardiac disease (unstable angina), uncontrolled hypertension, congestive cardiac failure, ventricular arrhythmias, active ischemic heart disease, myocardial infarction within 6 months, chronic liver or renal disease, active upper gastrointestinal tract ulceration).
- Any psychological, familial, sociological, or geographical condition potentially hampering

compliance with the study protocol and follow-up schedule; such conditions were to be discussed with the patient before registration in the trial.

- History of noncompliance to medical regimens or unwillingness or inability to comply with the protocol (especially 15-day biopsy, necessity to undergo breast surgery despite a clinical CR).
- Receipt of any other investigational drugs within the 30 days prior to the screening visit
- Treatment with drugs recognized as being strong inhibitors or inducers of the isoenzyme cytochrome (CYP) 3A (rifabutin, rifampicin, clarithromycin, ketoconazole, itroconazole, voriconazole, ritinavir, telithromycin) within the last 5 days.

Number of Subjects

Patient disposition (ITT population)

	Everolimus + letrozole	Placebo + letrozole
Planned N	129	122
Completed n (%)	107 (82.9%)	113 (92.6%)
Dicontinued n (%)	22 (17.1%)	9 (7.4%)
Due to adverse events n (%)	13 (10.1%)	3 (2.5%)
Due to disease progression n (%)	1 (0.8%)	3 (2.5%)
Due to other reasons n (%)	8 (6.2%)	3 (2.5%)

Of the 251 randomized patients, 220 (87.6%) patients completed and 31 patients (12.4%) prematurely discontinued the study. A higher number of patients discontinued the study prematurely due to AEs in the everolimus + letrozole arm (10.1% vs. 2.5% in placebo arm) and to withdrawal of informed consent (4.7% vs. 0.8% in placebo arm).

Demographic and Background Characteristics

Demographic summary (ITT population)

	Everolimus + letrozole	Placebo + letrozole
N (ITT)	N=129	N=122
Mean age, years (SD)	67.7 (8.63)	66.4 (8.93)
Mean weight, kg (SD)	71.4 (13.77)	71.5 (13.60)
Gender – n (%) Female	129 (100)	122 (100)
Gender – n (%) Male	0	0
Race – n (%) Caucasian	127 (98.4)	122 (100)
Race – n (%) Back	1 (0.8)	0
Race – n (%) Other	1 (0.8)	0

Primary Objective Result(s)

Calculated overall response as determined by clinical palpation (ITT population)

	Everolimus + letrozole	Placebo + letrozole

	N=129	N=122
Tumor response	**n (%)**	**n (%)**
Complete response	18 (14.0)	11 (9.0)
Partial response	70 (54.3)	62 (50.8)
No change	33 (25.6)	37 (30.3)
Progressive disease	4 (3.1)	10 (8.2)
Not available/not evaluable	4 (3.1)	2 (1.6)
Overall response (CR + PR)	88 (68.2)	73 (59.8)
Chi-square test p-value		0.0832

Treatment effect adjusted for baseline prognostic factors logistic regression (ITT population)

		Odds Ratio		
Factor	**p value**	**Odds Ratio**	**95% CI**	**2- sided p value**
Treatment (Everolimus + letrozole vs. placebo + letrozole)	0.3403	1.14	0.61 – 2.12	0.6807
HER2+ (no vs. yes)	0.6423	0.84	0.34 – 2.11	0.7154
Baseline tumor size (< 5 cm vs.> 5 cm)	0.0899	1.69	0.79 – 3.62	0.1799
Baseline nodes (no vs. yes)	0.2354	1.27	0.66 – 2.46	0.4709
Planned surgery (breast conserving vs. mastectomy)	0.3931	1.10	0.57 – 2.12	0.7861

Treatment effect adjusted for baseline prognostic factors excluding HER2+-sensitivity analysis (ITT population)

		Odds Ratio		
Factor	**p value**	**Odds Ratio**	**95% CI**	**2- sided p value**
Treatment (Everolimus + letrozole vs. placebo + letrozole)	0.0850	1.44	0.85 – 2.43	0.1701
Baseline tumor size (≤ 5 cm vs.≥ 5 cm)	0.1306	1.46	0.75 – 2.84	0.2611
Baseline nodes (no vs. yes)	0.3315	1.13	0.65 – 1.97	0.6629
Planned surgery (breast conserving vs. mastectomy)	0.3554	1.11	0.65 – 1.90	0.7108

Secondary Objective Result(s)

Overall response as determined by ultrasound (ITT population)

	Everolimus + letrozole N=129			Placebo + letrozole N=122			Total N=251		
Overall response	**n**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**
Complete response	6	(4.7)		0			6	(2.4)	
Partial response	71	(55.0)		58	(47.5)		129	(51.4)	
No change	39	(30.2)		53	(43.4)		92	(36.7)	
Progressive disease	4	(3.1)		6	(4.9)		10	(4.0)	
Not available/not evaluable	9	(7.0)		5	(4.1)		14	(5.6)	
Overall response (CR + PR)	77	(59.7)	(51.2, 68.2)	58	(47.5)	(38.7, 56.4)	135	(53.8)	(47.6, 60.0)
Chi-square test p-value					0.0268				

Tumor response is calculated using tumor change from baseline measurements measured by breast ultrasound.

Response is calculated from the Month 4 assessment. If this is missing than the last non-missing tumor assessment is used.

Patients with missing baseline or having no post-baseline measurements are considered non- evaluable.

The 95% Confidence Intervals are calculated using the normal approximation to the binominal distribution.

Chi-square test without continuit correction (significance threshold: 1 sided p-value ≤ 0.10).

Overall response as determined by mammography (ITT population)

	Everolimus + letrozole N=129			Placebo + letrozole N=122			Total N=251		
Tumor response	**n**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**
Complete response	12	(9.3)		8	(6.6)		20	(8.0)	
Partial response	35	(27.1)		40	(32.8)		75	(29.9)	
No change	54	(41.9)		53	(43.4)		107	(42.6)	
Progressive disease	2	(1.6)		6	(4.9)		8	(3.2)	
Not available/not evaluable	26	(20.2)		15	(12.3)		41	(16.3)	
Overall response (CR + PR)	47	(36.4)	(28.1, 44.7)	48	(39.3)	(30.7, 48.0)	95	(37.8)	(31.8, 43.8)
Chi-square test p-value					0.6826				

Tumor response is calculated using tumor change from baseline measurements measured by mammography.

Response is calculated from the Month 4 assessment. If this is missing than the last non-missing tumor assessment is used.

Patients with missing baseline or having no post-baseline measurements are considered non- evaluable.

The 95% Confidence Intervals are calculated using the normal approximation to the binominal distribution.

Chi-square test without continuity correction (significance threshold: 1 sided p-value ≤ 0.10).

Safety Results

As was expected, there were markedly more AEs in the everolimus treated patients, as compared to placebo treated patients. This is reflected in a higher rate of early discontinuations of study therapy in the everolimus + letrozole arm (10.2% vs. 2.5%). AEs requiring dose adjustment or study-drug interruption were markedly more frequent in the everolimus + letrozole (58.6%) than in the placebo + letrozole arm (7.4%). Stomatitis and rash were frequent AEs requiring dose reduction or interruption of everolimus (11.7% and 4.7%). Stomatitis was mostly mild to moderate, with only 3 patients (2.3%) experiencing grade 3 stomatitis. Rash also was mostly mild to moderate, with only 1 patients (0.8%) experiencing grade 3 rash. Most frequent hematological AEs requiring dose reductions of everolimus were neutropenia (6.3%) and thrombocytopenia (5.5%). Most frequent biochemistry laboratory abnormalities requiring dose reduction were ALT increase (6.3%) and hyperglycemia (6.3%).

Six patients in the everolimus + letrozole arm had clinically notable pulmonary events (4.7%). Of those, two cases (1.6%) of grade 3 interstitial lung disease were observed. In addition, there was one case of grade 3 and one case of grade 2 pneumonitis in this arm, one case of grade 2 allergic alveolitis, and one case of grade 1 lung infiltration was also seen in this arm. None of these respiratory disorders occurred in the placebo + letrozole arm. A total of 3 patients (2.3%) in the everolimus + letrozole arm had a dose reduction because of cough, and 2 patients (1.6%) had a dose reduction because of dyspnea. No dose reductions for respiratory disorders were required in the placebo + letrozole arm.

The safety profile of everolimus in combination with letrozole is acceptable in the context of neoadjuvant therapy for breast cancer, given the higher response rate. The majority of adverse events were of mild to moderate degree, and reversible after dose reduction or discontinuation of everolimus. The nature and frequency of adverse events observed in the everolimus + letrozole arm are consistent with data for everolimus monotherapy. Stomatitis and rash were the most frequent clinically detectable adverse events requiring dose reduction or discontinuation of everolimus. Monitoring of blood count, blood glucose, ALT/AST and serum lipids would detect the most frequent laboratory abnormalities associated with everolimus treatment. Newly occurring cough and/or dyspnea may be symptoms of everolimus-associated non infectious pneumonitis and should be followed up radiologically and clinically.

Adverse Events by System Organ Class

Adverse events by system organ class (Safety population)

	Everolimus + letrozole N=128	**Placebo + letrozole N=122**
System organ class	**n (%)**	**n (%)**
Patients with any AE	122 (95.3)	82 (67.2)
Gastrointestinal disorders	78 (60.9)	32 (26.2)
Skin and subcutaneous tissue disorders	62 (48.4)	16 (13.1)
Metabolism and nutrition disorders	56 (43.8)	21 (17.2)
General disorders and admin. site conditions	55 (43.0)	23 (18.9)
Infections and infestations	46 (35.9)	17 (13.9)
Blood and lymphatic system disorders	46 (35.9)	5 (4.1)
Investigations	39 (30.5)	12 (9.8)
Nervous system disorders	30 (23.4)	13 (10.7)
Respiratory, thoracic and mediastinal disorders	29 (22.7)	10 (8.2)
Musculoskeletal and connective tissue disorders	22 (17.2)	24 (19.7)
Vascular disorders	21 (16.4)	25 (20.5)
Psychiatric disorders	18 (14.1)	13 (10.7)
Eye disorders	7 (5.5)	3 (2.5)
Injury, poisoning and procedural complications	5 (3.9)	4 (3.3)
Reproductive system and breast disorders	5 (3.9)	8 (6.6)
Cardiac disorders	5 (3.9)	3 (2.5)
Renal and urinary disorders	3 (2.3)	0
Ear and labyrinth disorders	2 (1.6)	2 (1.6)
Hepatobiliary disorders	2 (1.6)	0
Neoplasm benign, malignant and unspecified	0	1 (0.8)

Most Frequently Reported AEs Overall by Preferred Term n (%)

Frequent adverse events reported in everolimus + letrozole by preferred term

Preferred term	**Everolimus + letrozole N=128 n (%)**
Patients with any AE	122 (95.3)
Stomatitis	50 (39.1)
Rash	28 (21.9)
Thrombocytopenia	25 (19.5)
Asthenia	24 (18.8)
Hypercholesterolemia	22 (17.2)
Hyperglycemia	18 (14.1)

Pruritus	18 (14.1)
Fatigue	17 (13.3)
Anorexia	17 (13.3)
Alanine aminotransferase increased	16 (12.5)
Anemia	16 (12.5)
Hot flush	15 (11.7)
Headache	15 (11.7)
Diarrhea	13 (10.2)
Neutropenia	13 (10.2)

Frequent adverse events reported in Placebo + letrozole by preferred term

Preferred term	**Placebo + letrozole N=122 n (%)**
Patients with any AE	82 (67.2)
Hot flush	22 (18.0)
Asthenia	13 (10.7)
Arthralgia	12 (9.8)
Nausea	11 (9.0)
Rash	10 (8.2)
Stomatitis	8 (6.6)
Hypercholesterolemia	8 (6.6)
Headache	7 (5.7)
Fatigue	6 (4.9)
Anorexia	5 (4.1)
Alanine aminotransferase increased	5 (4.1)
Aphthous stomatitis	5 (4.1)
Hyperglycemia	4 (3.3)
Dysgeusia	4 (3.3)
Insomnia	4 (3.3)
Pain in extremity	4 (3.3)

Serious Adverse Events and Deaths

Deaths, other serious and clinically significant adverse events (Safety population)

	Everolimus + letrozole N=128 n (%)	**Placebo + letrozole N=122 n (%)**	**Total N=250 n (%)**
Deaths	0	0	0
SAEs	15 (11.7)	6 (4.9)	21 (8.4)
Study drug-related SAEs	7 (5.5)	1 (0.8)	8 (3.2)
Study drug-related AEs	115 (89.8)	53 (43.4)	168 (67.2)
Grade 3 or 4 AEs	30 (23.4)	5 (4.1)	35 (14.0)
Discontinuations due to AEs	13 (10.2)	3 (2.5)	16 (6.4)

AEs causing dose adjustment/interruption	75 (58.6)	9 (7.4)	84 (33.6)

Other Relevant Findings

None

Date of Clinical Trial Report

01-April-2008 (CSR original)

29-Jul-2011 (CSR rerun)

Date Inclusion on Novartis Clinical Trial Results Database

1-Dec-2011

Date of Latest Update