Sponsor

Novartis

Generic Drug Name

Letrozole

Therapeutic Area of Trial

Endometrial Cancer

Approved Indication

Indicated for the treatment of

- Adjuvant treatment of post menopausal women with hormone receptor positive (HR+) early stage breast cancer.
- Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy
- First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer.

Study Number

CFEM345ADE08

Title

Phase II Study on Letrozole in patients with advanced or recurrent hormone receptor positive endometrial cancer.

Phase of Development

II

Study Start/End Dates

27 Apr 2005 to 14 May 2010

Study Design/Methodology

The study was designed as a prospective, single group, multicenter phase II study according to A´Hern on the efficacy and tolerability of a treatment with Letrozole 2,5mg administered orally daily.

The study population consisted of women with advanced or recurrent hormone receptor positive endometrial cancer treated with the selective aromatase inhibitor Letrozole. The primary variable was the rate of patients who reached partial or complete response (PR and CR) according to RECIST at least once during the treatment period. Since progestin therapy is not curative in this

situation, and only a minority of patients showed response to it, both women without previous and those with one previous progestational hormone treatment for recurrence were eligible for the study.

It was assumed that the chosen regimen would be of no further interest in endometrial cancer if the tumor response rate (CR, PR) is less than 5%. It was also assumed that a response rate of 20% or more would be of considerable interest in patients with this disease. The null hypothesis (H_0) that the true response rate is ≤ 5% is tested versus the alternative hypothesis (H_A) that the true response rate is ≥ 20%. The therapy would be regarded interesting for further evaluation if there would be at least 5 responders among 38 evaluable patients. Considering a drop-out rate of 10 % a total of 42 patients would have to be enrolled in the study centers.

Patients entered the treatment by oral dose of 2.5 mg of Letrozole per day. The treatment did not require hospitalization and was given as an outpatient treatment. The treatment was administered until documented disease progression, unacceptable toxicity at the discretion of the investigator or patient refusal.

The patients were treated until disease progression and were followed up until survival for upto 12 and 24 months. Efficacy and safety of the study drug was assessed every 3 months during the on-treatment period. The assessment to address the primary objective was performed at the end of the on-treatment period.

Altogether 42 patients were planned to be accrued in order to reach 38 evaluable patients. However, due to slow recruitment, enrolment was stopped after 27 patients. Consequently, the results were interpreted only explorative as there was not sufficient power with this sample size to achieve the proposed response.

Centres

8 centres in Germany

Publication

None

Objectives

Primary objective(s)

- To evaluate the response in women with advanced or recurrent hormone receptor positive endometrial cancer treated with the selective aromatase inhibitor Letrozole, i.e. response rate of patients who reached partial or complete response (PR and CR) according to RECIST criteria at least once during the treatment period.

Secondary objective(s)

To evaluate:

- Time to progression
- Overall survival
- Treatment safety

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

Letrozole 2.5 mg once daily orally.

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

None

Criteria for Evaluation

Primary variables

- Rate of patients who reached partial or complete response (PR and CR) according to RECIST at least once during the treatment period.

Secondary variables

- Frequency of adverse events and other laboratory values
- Time to progression
- Overall survival

Safety and tolerability

- As discussed under secondary variables

Pharmacology

- Not applicable

Statistical Methods

The null hypothesis (H_0) that the true response rate is ≤ 5% is tested versus the alternative hypothesis (H_A) that the true response rate is ≥ 20%. The significance level (i.e., the probability of rejecting H_0 when it is true) is 0.05. The power (i.e., the probability of deciding the regimen is active) is 0.90.

The study was designed according to A´Hern: The therapy was to be regarded interesting for further evaluation if there had been at least 5 responders (i.e. patients with PR or CR at least once) among the 38 evaluable patients. However, due to slow recruitment the study was stopped after enrolling 27 patients. All analyses are strictly explorative.

The primary efficacy variable was analyzed in an exploratory manner with the 95% confidence interval for the response rate on intent-to-treat population.

Additionally, the rate of patients who reached partial or complete response at least once during the treatment period or who had stable disease was presented with the 95% confidence interval.

Time to progression was calculated as time from first drug intake until time of progression, presented as a Kaplan-Meier curve.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Women with documented advanced or recurrent hormone receptor positive endometrial cancer were enrolled into the study. Patients may have failed 1 prior progestin therapy or be considered for Letrozole as first-line treatment of advanced / recurrent disease. Prior chemotherapy was allowed.
- age ≥ 18 years
- presence of histologically proven adenocarcinoma or adenosquamous carcinoma of the endometrium
- presence of advanced or recurrent endometrial cancer, FIGO stage I-IV, incurable with surgery and/or radiation therapy
- Documented ER and/or PgR positive endometrial cancer. Hormone receptor positivity is defined according to routine practice at each participating laboratory.
- patient must be postmenopausal defined as
  - Age ≥55 years.
  - Age <55 but no spontaneous menses for at least 1 year.
  - Age <55 and spontaneous menses within the past 1 year, but currently amenorrheic (e.g., spontaneous or secondary to hysterectomy), and with postmenopausal gonadotrophin levels (luteinizing hormone and follicle stimulating hormone levels >40 IU/L) or postmenopausal estradiol levels (<5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.
  - Bilateral oophorectomy
  - Radiation menopause.
- presence of measurable disease (by clinical/radiological examination – according to RECIST criteria : minimum indicator lesion size : 20 mm (unless spiral CT scan in which case > 10 mm)
- ECOG performance status of 0, 1 or 2
- adequate bone marrow function (WBC ≥ 3.5 x 10^9/L and platelets ≥ 100.0 x 10^9/L) and hemoglobin > 10.0 g/dl
- adequate renal function (creatinine < 120 µmol/L) and hepatic function (bilirubin < 25

µmol/L, AST (SGOT < 60 U/L)

- minimum life expectancy of at least 6 months
- patients who are accessible for treatment and follow-up

Exclusion Criteria:

- presence of non-measurable disease only
- other concomitant anti-cancer treatment (except XRT for symptomatic metastatic lesions if other assessable untreated lesions are present)
- prior treatment with aromatase inhibitors or anti-estrogens (up to one previous progestational hormone therapy regimen for recurrent disease was permitted)
- clear cell or papillary serous histology, uterine sarcomas, mixed Mullerian tumors (MMT) and/or adenosarcomas
- other concurrent malignant disease with the exception of cone-biopsied *in situ* carcinoma of the cervix uteri, or adequately treated basal or squamous cell carcinoma of the skin, or other curable cancers e.g. Hodgkin`s disease or NHL, provided 5 years had elapsed from completion of therapy, and there had been no recurrence
- known CNS metastases, bilateral diffuse lymphangiosis carcinomatosa of the lung (>50 % of lung involvement, or dyspnea at rest requiring supplemental oxygen therapy), evidence of metastases estimated as more than a third of the liver as defined by sonogram and/or CT scan
- uncontrolled endocrine disorders such as diabetes mellitus, confirmed hypo- or hyperthyroidism, Cushing`s Syndrome, Addison`s disease (treated or untreated)
- unstable angina and uncontrolled cardiac disease
- treatment with other investigational drugs (drugs not marketed for any indication) within the past 30 days and/or the concomitant use of investigational drugs
- a history of non-compliance to medical regimens
- inability to swallow pills

Number of Subjects

Patient disposition

		Total (N=27) n (%)
Study completion	Treated	27 (100.0)
	Discontinued	5 (18.5)
	Completed	22 (81.5)
Reason for discontinuation	Adverse event(s)	2 (7.4)
	Patient withdrew consent	3 (11.1)

Demographic and Background Characteristics

Demographic characteristics by treatment group for the ITT population

		Total
Variable	Statistic	(N=27)*
Age [yrs]	Mean	71
	SD	6.2
	Min	60.0
	Median	69
	Max	84.0
< 65 years	n (%)	4 (14.8)
≥ 65 years	n (%)	23 (85.2)
* All were Caucasian female patients		

Primary Objective Result(s)

Disease control rate in the ITT population

	(N=27)		
	n	(%)	95 % CI [% - %]
Stable disease (disease control rate)	10	(37.0)	[18.8 - 55.3]

None of the patients reached the primary endpoint. 37% of patients reached SD at least once during the study.

Secondary Objective Result(s)

Number (%) of patients with most frequent AEs (10% or more of the patients)

System organ class			
Preferred term	**n**	**% of patients (n=27)**	**% of all AEs**
All System Organ Classes			
No. of Patients with AEs	26	(96.3)	
Total no. of AEs	99		(100.0)
Anemia	6	(22.2)	(6.1)
Abdominal pain	5	(18.5)	(5.1)
Constipation	4	(14.8)	(4.0)
Diarrhea	3	(11.1)	(3.0)
Nausea	5	(18.5)	(5.1)
Fatigue	8	(29.6)	(8.1)
General physical health deterioration	3	(11.1)	(3.0)
Urinary tract infection	3	(11.1)	(3.0)
Weight decreased	3	(11.1)	(3.0)
Arthralgia	5	(18.5)	(5.1)
Sleep disorder	3	(11.1)	(3.0)
Hot flush	4	(14.8)	(4.0)

Most frequent AE (by preferred term) were `Fatigue (29.6%), and anemia (22.2%).

Safety Results

As discussed under secondary objectives.

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them

	TOTAL	
	No. (%) of AEs	**No. (%) of patients (n=27)**
All AEs	99 (100.0)	26 (96.3)
With suspected drug relation	16 (16.2)	9 (33.3)
Leading to dose adjustment or temp. interruption	0 (0.0)	0 (0.0)
Leading to permanent discontinuation	4 (4.0)	2 (7.4)
Requiring concomitant medication/non-drug therapy	35 (35.4)	13 (48.1)
Serious AEs	13 (13.1)	6 (22.2)
Deaths		0 (0.0)
SAEs with suspected drug relation	0 (0.0)	0 (0.0)
SAEs leading to permanent discontinuation	0 (0.0)	0 (0.0)

Other Relevant Findings

Follow up phase median survival time was 383 days

Date of Clinical Trial Report

08 Mar 2011

Date Inclusion on Novartis Clinical Trial Results Database

12 Apr 2011

Date of Latest Update