STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Arimidex
ACTIVE INGREDIENT: Anastrozole

Study No: NIS-OES-ARI-2004/1
Assessment of endometrial changes in postmenopausal women with breast cancer in adjuvant treatment with Anastrozole.

Developmental phase: Not applicable
Study Completion Date: 27-02-2009
Date of Report: 15-01-2010

OBJECTIVES:

Primary Objective

The primary objective of the study is to know the global incidence of endometrial alterations during the adjuvant treatment with Anastrozole

Secondary Objectives

The secondary objectives are:

- To describe the endometrial alterations from both a clinical (presence of endometrial bleeding) and an ecographical point of views
- In the indicated cases, from a gynaecological point of view, a histological study will be done classifying the results in:
    - Serious: atypical hyperplasia, polyp with atypia and cancer
    - Non-serious: simple hyperplasia and polyp without atypia
- To evaluate the global incidence of endometrial pathology in the postmenopausal population with early breast cancer before starting the hormonal treatment with Anastrozole.
- To evaluate the nature of medical interventions required to endometrial anomalies, including the hysterectomies rate.
- To evaluate the tolerability of the drug

METHODS:

Observational, open, prospective and multicentre study in a cohort of postmenopausal patients diagnosed of primary breast cancer with positive hormonal receptors and with adjuvant hormonal treatment with Anastrozole for 5 years.

The study observation period was extended up to one year after withdrawal of the adjuvant medication (caused by the end of treatment after 5 years or by disease progression before ending these 5 years of treatment or by intolerance to Anastrozole).

For an accumulated incidence at 2 years of 9% of endometrial alterations with Anastrozole, a sample size of 504 patients could estimate this incidence with a precision of +/-2.5% with a confidence interval of 95%. Assuming a 20% of lost patients the sample size would be 630 patients.

The study recruitment was initially planned for one year, however, after more than 20 months only 154 patients were recruited and the decision of stopping recruitment and follow-up was made. So no conclusion can be made regarding endometrial changes incidence during the adjuvant treatment with Anastrozole.

RESULTS:

There were 145 patients included. Mean age was 63.87 years, range (37.10, 88.53). Sixty per cent of patients had, at least, either a concomitant disease or concomitant treatment. Breast cancer antecedent was done in a 41.38% and endometrial cancer in a 2.07% of patients. Mean time from menarche to menopause was 41.35 years.

The most often G-A-L parity was 2-0-2 (24.37% of patients). A 7.19% had substitutive hormonal treatment and this was estrogenic treatment in a 77.78% of patients.

	All patients (N=145)	95%CI
TNM Classification(*)		
I	62(43.66%)	(35.36%,52.23%)
IIA	39(27.46%)	(20.32%,35.58%)
IIB	24(16.90%)	(11.14%,24.10%)
IIIA	11(7.75%)	(3.93%,13.44%)
IIIB	1(0.70%)	(0.02%, 3.86%)
IIIC	5(3.52%)	(1.15%, 8.03%)
Missing	3	-
Anatomopathological Diagnosis, N(%)		
Ductal Carcinoma in situ	4(2.88%)	(0.79%, 7.20%)
Infiltrant Ductal Carcinoma	108(77.70%)	(69.86%,84.32%)
Lobular Carcinoma in situ	11(7.91%)	(4.02%,13.72%)
Infiltrant Lobular Carcinoma	15(10.79%)	(6.17%,17.17%)
Ductal and Lobular Carcinoma in situ	1(0.72%)	(0.02%, 3.94%)
Estrogen Receptor Positive, N(%)		
Yes	137(94.48%)	(89.42%,97.59%)
No	8(5.52%)	(2.41%,10.58%)
Progesterone Receptor Positive, N(%)		
Yes	112(78.32%)	(70.66%,84.77%)
No	31(21.68%)	(15.23%,29.34%)
Missing	2	-
Patients erbB2 positive, N (%)		
Yes	36(28.57%)	(20.88%,37.30%)
No	90(71.43%)	(62.70%,79.12%)
Missing	19	-

(*) American Joint Committee on Cancer (AJCC) classification.

Tabla 1 Neoadjuvant and/or adjuvant treatment		
	All patients (N=145)	**95%CI**
Radiotherapy, N(%)		
Yes	85 (59.44%)	(50.92%,67.56%)
No	58 (40.56%)	(32.44%,49.08%)
Missing	2	-
Chemotherapy, N(%)		
Yes	69 (49.29%)	(40.74%,57.86%)
No	71 (50.71%)	(42.14%,59.26%)
Missing	5	-
Tamoxifen treatment before surgery, N(%)		
Si	0 (0.00%)	-
No	142 (100.00%)	-
Missing	3	-
Patients with Tamoxifen+adjuvant stopped by toxicity, N(%)		
Si	13 (9.03%)	(4.89%,14.94%)
No	131 (90.97%)	(85.06%,95.11%)
Missing	1	-

Primary Objective

The endometrial alterations rate (excluding baseline visit) was 2.76% (95%CI [0.76%,6.91%]).

Table 1 Endometrial Alterations		
Variable	**All patients (N=145)**	**95%CI**
At least one endometrial alteration, N(%)		
Yes	4(2.76%)	(0.76%, 6.91%)
No	141(97.24%)	(93.09%,99.24%)

Secondary Objectives

A 5.52% of patients had at least one abnormal gynaecological exploration, a 2.07% had vaginal bleeding, and an 8,28% had an abnormal ecography. Regarding endometrial thickness, in a 27.59% of patients was less than 5 mm, in a 12.41% of patients was between 5 and 7 mm, in one patient was between 7 and 10 mm, and in another patient was more than 10 mm. A 40.69% of patients had a homogeneous and

a 2.76% had a heterogeneous endometrial texture. And a 5.52% of patients had at least one exploration with polyps.
No patients had a serious biopsy result (atypical hyperplasia, polyp with atypia or cancer) and only one patient had a non-serious biopsy result (simple hyperplasia or polyp without atypia)
The baseline endometrial alterations rate was 6.21% (95%CI [2.88%,11.46%]).

Only one patient (0.69%) had a hysterectomy done during the study.

Tolerability

Regarding adverse events (AE) occurred during the study, a 37.24% of patients had at least one AE, a 34.48% had at least one AE related to the drug, a 28.28% had at least one mild AE, a 10.34% had at least one moderate AE and a 5.52% had at least one severe AE, a 28.28% had at least one mild related AE, a 9.66% had at least one moderate related AE and a 2.76% had at least one severe related AE, a 2.76% had at least one serious AE and a 2.07% had at least one AE with outcome as death.

Adverse Events	Adverse Events (N=145)	Drug related Adverse Events
Joint pain/stiffness	32 (27.27%)	32 (27.27%)
Hot flushes	16 (14.55%)	16 (14.55%)
Asthenia	15 (13.64%)	15 (13.64%)
Hypercholesterolemia	12 (10.91%)	12 (10.91%)
Headache	8 (7.27%)	8 (7.27%)
Nausea	7 (5.45%)	6 (5.45%)
Alopecia	4 (3.64%)	4 (3.64%)
Rash	3 (2.73%)	3 (2.73%)
Anorexia	2 (1.82%)	2 (1.82%)
Vaginal bleeding	2 (1.82%)	2 (1.82%)
Arthralgia	1 (0.91%)	1 (0.91%)
Death	1 (0.91%)	-
Subdural Haematoma	1 (0.91%)	-
Myocardial infarct	1 (0.91%)	-
Paresthesias	1 (0.91%)	1 (0.91%)
Progression disease	1 (0.91%)	-
Somnolence	1 (0.91%)	1 (0.91%)
Tendinitis	1 (0.91%)	-
Vomiting	1 (0.91%)	1 (0.91%)