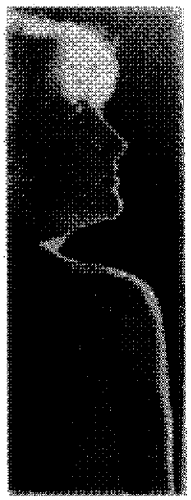

22nd Annual San Antonio Breast Cancer Symposium

DECEMBER 8-11, 1999

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Symposium Dates

2000:	December 6-9
2001:	December 10-13
2002:	December 11-14
2003:	December 3-6
2004:	December 8-11

Abstract Submission Deadline: June 1 every year

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25 RANDOMISED DOUBLE-BLIND PHASE 2 STUDY OF A SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERM) LY353381 IN PATIENTS (Pts) WITH LOCALLY ADVANCED OR METASTATIC BREAST CANCER (LAMBC).

Baselga J[1]*, Llombart-Cussac A[2], Bellet M[1], Guillem-Porta V[2], Petruzelka L[3]. [1]Sanitaria Vall D'Hebron, Barcelona 08036, Spain; [2]Instituto Valencia de Oncologia, Valencia, 46009, Spain; [3]1st Medical Faculty, Charles University, Prague, Czech Republic. On behalf of the Study Group.

LY353381 is a new SERM which pre-clinical studies have shown to be a potent antagonist in breast and endometrial models with beneficial agonist properties on bone and lipids. We performed a Phase 2 trial to investigate the activity of LY353381 in LAMBC with randomisation between 20 mg or 50 mg per day. Eligibility criteria included; Zubrod PS of 0-1, estrogen and/or progesterone receptor positivity (ER/PR), adequate major organ function and no prior systemic therapy for LAMBC. Prior adjuvant tamoxifen (tam) was permitted provided it had stopped ≥ 12 months (mo) before study entry. Pts were stratified for prior tam, degree of ER positivity and the extent of metastatic involvement. Ninety-two pts were randomised between the two dose levels in a double-blind fashion and interim data is available on 87 pts. Median age was 70 years (range 37-94), PS 0 (55/87) and 1(32/87) with 7 pts peri- and 80 post-menopausal. Median time from diagnosis to study entry was 1 mo (range 0-251), 18/87 received prior adjuvant chemotherapy and 8/87 had adjuvant tam. Disease status at study entry was Locally Advanced (LA) in 31/87 and 56/87 were classified as metastatic. Dominant disease sites were skin and soft tissue (32/87), visceral (31/87), bone (16/87) and node only (8/87). Median time on therapy is currently 3 mo (range 1-9 mo) and responses have been seen in pts with MBC as well as those with LA disease only. The major side effect seen to date is hot flushes with 20/81 and 9/81 patients with grade 1 or 2 severity, respectively. Other toxicities are minimal although lymphopenia has been noted in 13 patients (G1 5/81, G2 7/81 and G3 1/81). Whilst follow-up is limited, preliminary data on 55 patients currently evaluated at 3 mo include 10 confirmed PRs (WHO criteria) in addition to 10 PRs and 2CRs needing 4 week confirmation. Only 3 patients have been discontinued for PD before the 3 mo visit. LY353381 is also extremely well tolerated. Data analyses are ongoing and full, unblinded results between the two dose levels will be presented.

26 EFFECT OF RALOXIFENE ON KI67 AND APOPTOSIS.

Dowsett M[1*], Lu Y[2], Hills M[1], Bundred N[3], Costa A[4], Decensi A[4], Sainsbury R[5], O'Brien M[6], Scott T[2], Muchmore DB[2]. [1]Royal Marsden NHS Trust, London, England; [2]Eli Lilly and Company, Indianapolis, IN; [3]Whithington Hospital, Manchester, England; [4]European Institute of Oncology, Milan, Italy; [5]Huddersfield Royal Infirmary, Huddersfield, England; [6]Mid Kent Oncology Centre, Maidstone, England.

Raloxifene (RLX) is a benzothiophene selective estrogen receptor modulator (SERM) that has been approved in the US for the prevention of postmenopausal osteoporosis. This double-blind study was performed to assess the effects of RLX on intermediate endpoint markers in human breast cancer. 167 postmenopausal women less than 80 years of age with a new diagnosis of stage I or II primary breast cancer were randomly assigned to 14 days of therapy with placebo, RLX 60 mg/d or RLX 600 mg/d. Baseline evaluation of a core biopsy (at least 14 gauge needle) included measurement of Ki67, apoptosis, estrogen receptor (ER), and progesterone receptor (PR); these were repeated on tissue obtained from surgical resection of the primary tumor. 143 subjects (mean age, 66 years) had evaluable paired biopsy results. At baseline, 77% of subjects had stage I disease and 83% had ER+ tumors. Median percentage change from baseline to endpoint values are shown:

	Placebo N=44	RLX 60 N=50	RLX 600 N=49
Ki67	+5.1%	-15.4%*	-14.8%*
Apoptosis	+12.8%	+20.0%	0.00%
ER	-10.4%	-22.5%*	-28.0%*
PR	-2.7%	-3.6%	-8.4%

*p<0.05 compared with placebo (ANOVA)

Compared with placebo, RLX significantly reduced Ki67 and ER but did not significantly affect apoptosis or PR levels. Both doses of RLX had modestly greater differences in Ki67 in the ER+ subset of subjects. These results are consistent with the previously reported safety profile of RLX in osteoporosis clinical trials. However, available clinical data do not support use of RLX in breast cancer treatment or neoadjuvant therapy.

27 PRELIMINARY RESULTS OF TWO MULTI-CENTER TRIALS COMPARING THE EFFICACY AND TOLERABILITY OF ARIMIDEX™ (ANASTROZOLE) AND TAMOXIFEN (TAM) IN POSTMENOPAUSAL (PM) WOMEN WITH ADVANCED BREAST CANCER (ABC).

Nabholtz JM*, Bonneterre J, Buzdar AU, Thuerlimann BJK, Robertson JFR, Webster A, Steinberg M and von Euler M, on behalf of the 'Arimidex' Study Group. * Cross Cancer Institute, Edmonton, Canada.

'Arimidex' (anastrozole)(AN), a non-steroidal aromatase inhibitor is available for the treatment of ABC in PM women recurring/progressing on TAM treatment. Two clinical trials (carried out in USA / Canada [0030] and Europe / Rest of World [0027]) have compared the efficacy and tolerability of AN and TAM as first-line therapies in PM women with ABC. The trials were designed to allow combination of the data. The results of trial 27 have been reported previously (see Table below for summary). Here we report the efficacy results of trial 0030 alone and the combined analyses of 0030 and 0027. Both trials were randomized, double-blind, designed to demonstrate equivalent efficacy of AN 1 mg qd relative to TAM 20 mg qd in ER+ve and/or PR+ve or unknown patients eligible for hormonal therapy (HT). The primary endpoints of the trial were time to progression (TTP), objective response (OR) and tolerability. The results for trial 0030 and 0030/0027 are below:

Study 0030. 353 patients entered the trial and were followed for a median of 18 months. Disease progression (DP) was observed in 67% of AN patients and 76% of TAM patients. Median TTP was 11 months for AN and 5.6 months for TAM. OR (CR+PR) was 21% and 17% for AN and TAM respectively. Clinical benefit (CB) rates (CR+PR+SD ≥ 24 weeks) were 59% and 46% for AN and TAM respectively.

A total of 1021 patients (353 from 0030 and 668 from 0027), randomized on a 1:1 basis, were included in the combined analysis. DP was observed in 71% of AN patients and 76% of TAM patients. Median TTP was 8.5 months for AN and 7 months for TAM. OR was 29% and 27% for AN and TAM respectively. CB rates (CR+PR+SD ≥ 24 weeks) were 57% and 52% for AN and TAM respectively.

	Est Value 0027/0030/Comb	Lower 95% Conf Limit 0027/0030/Comb	Equiv Criterion
Haz Ratio (TTP) TAM/AN	0.99/1.44/1.12	0.86/1.16/1.00	0.80
Diff in OR (AN - TAM)	- 1%/+5%/+1%	- 7%/-2%/- 3%	-10%

*Arimidex' satisfied the pre-defined criteria for equivalent efficacy to TAM in each trial, and the combined analysis, with there being a suggestion of a numerical advantage with respect to TTP in the combined analysis and trial 0030. These data support the use of 'Arimidex' as an alternative treatment to TAM in PM women with ABC.

28 A PARTIALLY-BLIND, RANDOMISED, MULTICENTRE STUDY COMPARING THE ANTI-TUMOR EFFECTS OF SINGLE DOSES (50, 125, AND 250 MG) OF LONG-ACTING (LA) 'FASLODEX' (ICI 182,780) WITH TAMOXIFEN IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER PRIOR TO SURGERY.

[1]Robertson JFR, [2]Dixon M, [3]Bundred N, [4]Anderson E, [5]Dowsett M, [6]Nicholson R, [1]Ellis I. [1]City Hospital, Nottingham, [2]Western General Hospital, Edinburgh, [3]South Manchester University Hospital, Manchester, [4]Christie Hospital, Manchester, [5]Royal Marsden, London, [6]University College of Medicine, Cardiff, Wales, UK.

'Faslodex' (ICI 182,780) is the most advanced of a new class of drugs, the non-agonist ('pure'), steroidal anti-estrogens, currently in clinical trials in postmenopausal women with advanced breast cancer. Here, we report on the design of a partially-blind, randomised, multicentre study to compare the anti-tumor effects [upon estrogen receptors (ER), progesterone receptors (PR), 67 and apoptotic index (AI)], tolerability, and pharmacokinetics (PK) of LA, single-doses of ICI 182,780 (50 mg, 125 mg, and 250 mg) given intramuscularly (i.m) with tamoxifen and tamoxifen placebo in postmenopausal women prior to surgery for primary breast cancer.

Two hundred postmenopausal women with primary breast cancer (T1–T3; ER-positive or ER-unknown tumor) awaiting curative-intent resection surgery were recruited to the study. Patients had no prior treatment with tamoxifen, any other anti-hormonal therapy, radiotherapy, or neo-adjuvant chemotherapy for breast cancer; they were randomised (n= 40 per treatment arm) to receive a single i.m dose of ICI 182,780 (50, 125, or 250 mg), or oral tamoxifen (20 mg once daily) or matching tamoxifen placebo for 14 to 21 days. Biopsy samples, taken pre-treatment from the tumor and on the day of surgery (performed between days 15 and 22 of the study), were assessed for ER, PgR, Ki67, and AI. The PK profile was assessed at each dose level on Days 1, 3, 8, 11, 15, 22 , 29, 36, 43, 57, and 85. This study was designed as an exploratory trial, so the minimum power for statistical testing was set at 80% using a two-sided significance level of 5%, powered to detect differences in the tumor markers (ER, PgR, Ki67, and AI), and the tolerability and PK profiles. The findings of this study will be reported.

'Faslodex' is a trade mark, the property of Zeneca Ltd, a part of AstraZeneca

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