## O-21. LETROZOLE (FEMARA) IS A MORE EFFECTIVE INHIBITOR OF ESTROGEN ACTIVITY THAN TAMOXIFEN: EVIDENCE FROM A RANDOMIZED PHASE III TRIAL OF 4 MONTHS PREOPERATIVE ENDOCRINE THERAPY FOR POSTMENOPAUSAL WOMEN WITH PRIMARY INVASIVE BREAST CANCER

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**Background:** The agonist effects of tamoxifen (TAM) may limit efficacy against some breast cancers but the extent to which these agonist effects occur is unknown. To address this issue, changes in estrogen-regulated gene expression were monitored during preoperative endocrine therapy with either TAM or the aromatase inhibitor letrozole (LET).

**Methods:** Postmenopausal breast cancer patients received 4 months preoperative endocrine therapy with either LET or TAM in a double-blind phase III study. Biopsies were obtained pre and post treatment and assessed by immunohistochemistry (IHC) for expression of the estrogen-regulated proteins progesterone receptor (PgR, n = 223) and trefoil factor 1 (PS2, n = 219). Allred IHC scores were assigned and categorized as low (0–2), medium (3–5) and high (6–8). A change with treatment was recorded if the post treatment score changed category from pre treatment to cause an increase or decrease in expression category.

**Results:** A decrease in PgR category was more frequent with LET (65% LET vs 23% TAM). An increase in PgR level was more frequent with TAM (29% TAM vs 5% LET). Similar data were obtained with PS2 (p = 0.001, logistic regression). Study outcomes were superior for LET when compared with TAM. For a subset of patients with study biopsy confirmed ER and/or PgR positivity clinical response rates (CR + PR) were 60% for LET vs 41% TAM, p = 0.004 (Mantel-Haenszel (M-H)) and breast conservation occurred in 48% of patients treated with LET vs 36% on TAM, p = 0.036 (M-H).

**Conclusion:** Agonist effects on PgR and PS2 occur in about one third of cases treated with TAM and rarely with LET. LET was more effective in inducing regression of ER and/or PgR positive primary breast cancer than TAM.

## O-22. COMBINED USE OF GOSERELIN (ZOLADEX) AND ANASTROZOLE (ARIMIDEX) AS SECOND-LINE ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER – A STUDY OF ITS CLINICAL AND ENDOCRINE EFFECTS

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Sixteen premenopausal women with either metastatic (N = 13) or locally advanced primary breast cancer (N = 3) were treated with a combination of a gonadotropin releasing hormone (GnRH) agonist Zoladex (Z) and a third-generation aromatase inhibitor Arimidex (A). All had previously been treated with Z and tamoxifen (T).

**Clinical Effects:** Twelve women (75%) achieved objective response/stable disease (OR/SD) at 6 months with a median duration of remission of 17+ months (range: 6–47 months). Two remain in OR/SD.

**Endocrine Effects:** The introduction of Z + T resulted in an 89% reduction in serum oestradiol (E2) levels compared to pre-treatment ($p < 0.05$). Substitution of T by A on progression resulted in a further 76% fall ($p < 0.05$) (Table). Mean FSH levels were initially suppressed with Z + T falling from pre-Z + T levels of 10 to 1.6 IU/L ($p < 0.05$). Substitution of T by A led to a partial loss of this suppression with levels rising towards pre-treatment values (5.4 IU/L). LH levels were suppressed as would be expected by constant administration of a GnRH agonist. A non-significant fall from 0.34 to 0.20 pmol/L was seen when T was substituted by A. Testosterone, DHES and androstenedione, precursors in oestrogen synthesis pathway, showed small falls during treatment.

| | Pre-Z + T | 6 months on Z + T | 3 months on Z + A | 6 months on Z + A |
|---|---|---|---|---|
| Mean E2 (pmol/L) | 224 | 24 | 6 | 5 |

This study shows that Z + A induces therapeutic remission in a reasonable proportion of premenopausal women with advanced breast cancer who have progressed on Z + T. The clinical therapeutic effects are associated with demonstrable endocrine changes including a dramatic reduction of E2 levels seen in postmenopausal women receiving A alone. Further studies involving more patients and longer follow-up are warranted.

## O-23. ICI 182,780 ('FASLODEX') 250 MG MONTHLY INTRAMUSCULAR (I.M.) INJECTION SHOWS CONSISTENT PHARMACOKINETIC (PK) PROFILES WHEN GIVEN AS EITHER 1 x 5 ML OR 2 x 2.5 ML INJECTIONS IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER (ABC)

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ICI 182,780 ('Faslodex'™) (FAS) is an Estrogen Receptor Down-regulator that has been developed for use in the treatment of breast cancer. For therapeutic use, it is formulated as an oily solution for i.m. injection (LA formulation), slowly releasing FAS over a period of at least one month. In two phase III trials, postmenopausal patients with ABC were given FAS 250 mg, either as a 1 × 5 ml injection (trial 0020) or as 2 × 2.5 ml injections (trial 0021), once a month until disease progression.

Sixteen (trial 0020) and four (trial 0021) patients provided blood samples at intervals over 28 days for full PK profiles after the first injection. Thereafter monthly samples were obtained from 27 patients (trial 0020) and from all patients in trial 0021 (n = 194), and continued for up to 30 months (i.e., 30 injections) after the first dose.

The shape of the observed plasma FAS profiles following i.m. injection of the LA formulation was very similar in both studies. Gmean trough plasma concentrations increased slightly after the first injection from 2.4 ng/ml and 2.6 ng/ml, increasing to 6.5 ng/ml and 6.2 ng/ml in trials 20 and 21 respectively, reaching steady state after approximately three to six doses. Steady-state plasma FAS exposures ($AUC_{ss}$), was reached in 3–6 doses and predicted according to a structural model were very similar for both studies (trial 0020; 336 ng.d/ml, trial 0021; 294 ng.d/ml), and, by comparison with single dose data, represents approximately two-fold accumulation. The repeated i.m. injections were well tolerated in both studies. The results of this study show that 5 ml and 2.5 ml injections of FAS 250 mg are equally effective in maintaining plasma FAS levels in the therapeutic range for at least 30 months, and support the use of either dosing regimen in the clinical setting.

## O-24. ICI 182,780 ('FASLODEX'™) IS AT LEAST AS EFFECTIVE AS ANATROZOLE (ARIMIDEX™) IN POST-MENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER PROGRESSING ON PRIOR ENDOCRINE TREATMENT

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ICI 182,780 ('Faslodex'™) (FAS) is the first of a new class of anti-oestrogen: an Estrogen Receptor Downregulator. We report the results of two, randomised, multicentre, parallel-group trials, (0020 European and 0021 North American) comparing the efficacy and tolerability of a monthly intramuscular injection of 250 mg FAS with that of a daily oral administration of anastrozole (Arimidex™) (AN) 1 mg in post-menopausal (PM) women with advanced breast cancer (ABC) progressing on prior endocrine treatment. Primary endpoint was time to progression (TTP). Secondary endpoints included objective response (OR) rate, duration of response (DOR), and tolerability. Patients were recruited from 1997 to 1999 and randomly assigned to either FAS or AN. The median follow-up duration was 14.4 months (mo) for study 0020 and 16.8 months for study 0021, with disease progression in 83% of randomised patients. Both drugs had similar tolerability profiles and were well tolerated. The incidence of withdrawals due to a drug-related adverse event was 0.9% for FAS and 1.2% for AN. Data from all major efficacy endpoints are shown in Table.

| | 0020 | | 0021 | |
|---|---|---|---|---|
| | FAS | AN | FAS | AN |
| Median TTP (months) | 5.5 | 5.1 | 5.4 | 3.4 |
| OR (CR + PR) | 20.7% | 15.7% | 17.5% | 17.5% |
| Clinical Benefit Rates | 44.6% | 45% | 42.2 | 36.1 |
| Median DOR | 14.3 | 14.0 | 19.3 | 10.5 |

This is the first anti-oestrogen, which is at least as effective as the new generation aromatase inhibitor, AN in PM women with ABC and is especially noteworthy since most patients had had prior tamoxifen treatment. FAS will be a valuable additional treatment option for ABC in these patients.

## O-25. CORRELATION OF IMMUNOHISTOCHEMISTRY (IHC) AND GENE MICROARRAY ANALYSIS OF BREAST BIOPSIES FROM A PREOPERATIVE ENDOCRINE THERAPY TRIAL

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**Background:** IHC is used to assign predictive/prognostic marker status in breast cancer, but is limited by antibody availability. Microarray analysis rapidly evaluates expression of large numbers of genes and is a potentially efficient screen for identifying novel markers. However, for this purpose microarray and IHC assignment of standard markers must correlate.

**Methods:** Breast biopsies were collected before and after preoperative endocrine therapy from patients in a phase III trial comparing letrozole with tamoxifen. RNA was extracted from non-dissected frozen biopsies and converted to cRNA. Estrogen receptor (ER) and trefoil factor 1 (PS2) expression was determined with the FL Affymetrix array. ER and PS2 IHC were performed using standard methodology. Protein expression was scored by the Allred method (intensity + proportion); a score > 3 was considered positive.

**Results:** Expression profiles determined by array or IHC were scored as present and absent and expression levels were also recorded. IHC and gene expression profiles were available for 29 biopsies (17 pre- and 12 post-treatment) from 24 patients. The presence or absence of ER determined by array was concordant with IHC scored by the Allred method in 100% (29/29) of biopsies, however levels of ER mRNA measured by array did not correlate with IHC protein levels ($r = 0.267$, $p = 0.161$). Presence or absence of PS2 determined by array and IHC was concordant in 75% (21/28, 1 assay failure) of biopsies. A significant correla-