## 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.