O-12. EFFICACY OF TAMOXIFEN (TAM) FOLLOWING ANASTROZOLE (AN) AS FIRST-LINE TREATMENT FOR ADVANCED BREAST CANCER (ABC) IN POSTMENOPAUSAL (PM) PATIENTS (PTS)

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The aromatase inhibitor AN (Arimidex™) has shown efficacy and tolerability advantages compared with TAM for the first-line treatment of PM pts with ABC. The combined analysis of two multicentre randomised, double-blind trials (n = 1021) showed that among pts with hormone-sensitive tumours, AN treatment led to a significant prolongation of time to disease progression (p = 0.022). In order to assess the efficacy [regarding clinical benefit (CB) = CR + PR + SD ≥ 24 weeks and objective response (OR) = CR + PR] of AN or TAM as a second-line therapy following progression with the other, the subsequent unblinded treatment was recorded and evaluated from a questionnaire (>73% [n > 745] return by patients). Additional subgroup analysis was carried out to determine the impact of baseline characteristics, regarding the presence or absence of visceral metastases and hormone-receptor status on CB and OR. Overall and subgroup results are presented in the table. The overall results showed good and similar activity for TAM after AN and vice versa.

Overall population	TAM following AN		AN following TAM	
OR (no./total) (%)	12/137 (9)		7/134 (5)	
CB (no./total) (%)	58/137 (42)		54/134 (40)	
ER and/or PR status	Positive	Unknown/–	Positive	Unknown/–
OR (no./total) (%)	6/84 (7)	6/53 (11)	3/95 (3)	4/39 (10)
CB (no./total) (%)	35/84 (42)	23/53 (43)	39/95 (41)	15/39 (39)
Visceral metastases	Yes	No	Yes	No
OR (no./total) (%)	6/52 (12)	6/85 (7)	3/59 (5)	4/75 (5)
CB (no./total) (%)	22/52 (42)	36/85 (42)	21/59 (36)	33/75 (44)

These data support a previous study showing that AN is effective when given after TAM. Similar findings were seen for pts in all sub groups, but all benefit was greater in pts with ER and/or PR positive tumours and in those pts without visceral metastases.

O-13. THE EFFECT OF ANASTROZOLE (ARIMIDEX™) ON SERUM LIPIDS – A RANDOMIZED COMPARISON OF ANASTROZOLE (AN) vs TAMOXIFEN (TAM) IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER

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Anastrozole is a potent and selective non-steroidal aromatase inhibitor, which reduces estradiol levels in PM women to near undetectable values. A combined analysis of two trials in PM women with ABC has shown AN to have efficacy advantages (time to progression) over TAM in ER+ve patients (Buzdar et al. ASCO 2000 P154a, Abs 609D). The impact of AN and TAM on blood lipids was also monitored during these trials. Blood samples for lipid assessment [total cholesterol (TC), triglycerides, HDL, LDL, apoprotein A, apoprotein B, and lipoprotein a] were taken at baseline, 84, and 108 weeks. Preliminary blood lipid results are shown below. No major differences were seen for the other lipid endpoints.

Blood lipid	Baseline value [mmol/l (n)]		Mean change at 84 weeks (n)		Mean change at 108 weeks (n)	
	AN	TAM	AN	TAM	AN	TAM
TC	5.8 (476)	5.9 (511)	+0.3 (67)	−0.6 (55)	+0.3 (24)	−0.2 (31)
HDL	2.4 (306)	3.7 (304)	−1.0 (38)	−2.2 (36)	−2.1 (17)	−2.2 (23)
LDL	3.7 (306)	3.8 (304)	+0.2 (38)	−0.9 (36)	+0.1 (17)	−0.5 (23)

The effects of TAM were similar to that reported previously, but no major differences from effects of AN were observed. Despite its potent estradiol lowering properties, AN had no clinically detrimental effects upon blood lipids. These data suggest that clinical effects of AN due to any changes in lipid profiles are very unlikely.

O-14. TABLES OF ANTICIPATED BENEFIT FROM ADJUVANT THERAPY FOR THE INDIVIDUAL

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The relative risk (RR) reductions from adjuvant systemic hormonal (HT) and cytotoxic (CT) therapies are well established, by the meta-analysis process of the Early Breast Cancer Trialists Collaborative Group. However in advising the individual, benefit is best expressed as absolute (AB) rather than relative RR.

To estimate AB the RR reduction from therapy is applied to the patient's prognosis without therapy, with age correction for natural life expectancy. The most sensitive and specific predictor of prognosis is the Nottingham Prognostic Index (NPI).

For example for a woman of 45, the AB at 10 years from adjuvant polychemotherapy (PCT), expressed both as number extra alive (or) as women-years (w-y) gained:

NPI group	No PCT 10 yr OS %	PCT 10 yr extra alive %	w-y gained by 10 yrs	
			Total	Average/ women treated
Excel (EPG)	91	1	5	0.05
Good (GPG)	81	3	15	0.1
Mod (MPGI)	71	5	25	0.3
Mod (MPGII)	59	8	40	0.4
Mod (MPGIII)	39	11	55	0.6
Poor (PPG)	18	16	130	1.3

A woman in the PPG receiving PCT stands to gain an average 9 months extra of life (or) doubles her chance of 10 year survival.

A woman in the EPG gains 1 month on average (or) only a 1% improved 10 year survival chance.

Tables will be presented for HT (ER+) and CT, at ages 45, 55 and 65.

O-15. SURGEON WORKLOAD AND SURVIVAL OF BREAST CANCER PATIENTS

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The aim of this study was to determine the variation in surgeon workload over time and to assess the impact of workload on survival. This was a retrospective population-based study. Survival and multivariate analyses were used to assess 5-year survival and relative risk of death, adjusting for socio-economic and clinical variables. 16,092 breast cancer patients diagnosed and treated by surgery in the Yorkshire region between 1986 and 1994 were included in the study. Overall, surgeons with a low mean annual workload of less than 10 managed 6% of patients, surgeons with a workload of 10–29 treated 26%, 30–49 33%, while 35% were managed by surgeons with the highest workload of more than 50. Over the study period, there was a trend to increasing numbers of patients being treated by surgeons with higher workloads. During 1986–88, surgeons managing 50 or more patients per year treated 26% of cases. By 1992–94, this had increased to 42%.

Patients treated by the higher workload surgeons had significantly better survival. Survival 5 years from diagnosis was 58% in the lowest consultant workload category compared to 67% in the highest workload category. This difference could not be explained by differences in case-mix (age, disease extent, socio-economic profile and time period) or treatment. The findings suggest that management by surgeons with higher workloads have a positive effect on survival from breast cancer.

O-16. FACTORS UNDERLYING THE IMPROVEMENT IN MORTALITY FROM BREAST CANCER

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Possible reasons for the fall in mortality from breast cancer in the UK are earlier detection and adjuvant therapy.

Prognostic factors at presentation, the Nottingham Prognostic Index (NPI) and the 10 year case-survival (OS) have been examined for women diagnosed in 1980–1984 (prior to both the use of adjuvant therapy and the introduction of screening) and 1990–1994 (table).

Age 50+					
	1980–1984		1990–1994		
NPI	%	OS (n)	%	Expect. OS (n)	Ob. OS (n)
GPG	29.5	23.6	41.6	33.2	37.0
MPG	56.2	30.3	46.4	25.1	33.4
PPG	14.2	2.1	12.0	1.8	3.4
Total	100	56.0	100		73.8

In women aged 50–70 10 year OS rose from 56% to 74%. A higher percentage of cases in NPI Good Group (GPG) accounted for 13% of this (29% diminution in mortality).

Improvement occurred WITHIN the moderate group (MPG). The use of Tamoxifen accounted for 5% of the increase (14% diminution in mortality in those treated by Tamoxifen).

In women aged <50 survival rose from 57% to 74%. Earlier diagnosis accounted for only 3%, hormonal therapy (HT) for 9% and chemotherapy (CT) for 4% (a 47% fall in mortality for recipients of HT and 29.5% for recipients of CT).

O-17. A REVIEW OF AROMATASE INHIBITORS USED FOR NEOADJUVANT ENDOCRINE THERAPY

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Although neoadjuvant chemotherapy has been widely used, neoadjuvant endocrine therapy had been used much less frequently. In Edinburgh we have evaluated the aromatase inhibitors letrozole, anastrozole and exemestane and have now treated over 80 patients with these agents. Letrozole, anastrozole and exemestane have been shown in this initial small series of patients to produce a median reduction in tumour volume of >80%. Using ultrasound, all 3 aromatase inhibitors produced a median reduction in tumour volume of >75% compared to a 48% reduction in median volume in patients treated with tamoxifen. However, with these small number of patients, it was not possible to make any direct comparisons between different agents.

Following our initial observations a randomised trial was performed and reported with letrozole in 337 postmenopausal women with invasive breast cancer, all of whom had ER or PgR positive tumours and who were not eligible for breast conserving surgery. In an intention to treat analysis 154 were treated with letrozole 2.5 mg/day for 4 months and 170 with tamoxifen 20 mg/day for 4 months. Clinical response was 55% for letrozole versus 36% for tamoxifen, $p < 0.001$. Imaging responses confirmed the superiority of letrozole 35% versus 25% on ultrasound, $p = 0.042$ and 34% versus 16% on mammography, $p < 0.001$. Breast conserving surgery was possible in 45% treated by letrozole compared with 35% in the tamoxifen group, $p = 0.022$. Odds ratio for response to letrozole was 6.5 if the tumour was ER positive versus 5.3 for tamoxifen. It has also been reported in patients who were erbB1 and/or erbB2 positive the odds ratio of a response was 28 in favour of (4.5–177) responding to letrozole compared with tamoxifen. This study demonstrates letrozole is superior to tamoxifen in the neoadjuvant setting. Further studies are ongoing with other aromatase inhibitors. Currently, an aromatase inhibitor is the neoadjuvant endocrine agent of choice in postmenopausal women with ER positive breast cancers.