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O-1 Long-term mortality results from the UK Breast Screening Frequency Trial

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In the UK Breast Screening Frequency Trial, 49173 women aged 50–62 were randomised to three annual incidence screens after their prevalence screen date (study group) and 50162 to one incidence screen three years after the prevalence screen (control group).
Primary interest was in those who attended the prevalence screen. Results of predicted case survival based on the Nottingham Prognostic Index of the tumours diagnosed have already been published, indicating an insignificant 5–11% reduction in breast cancer mortality.
Here we present actual mortality results to the end of 2006 (median follow-up 162 months). There were 373 breast cancer deaths in the study group as a whole and 374 in the control group (RR = 1.02, 95% CI 0.88–1.17, p = 0.8). In the prevalence screen attenders, there were 209 breast cancer deaths in the study group and 231 in the control group (RR = 0.89, 95% CI 0.73–1.07, p = 0.2).
When we consider mortality only from cancers diagnosed during the three-year screening period of the trial, there was no significant difference between the study and control group (RR = 0.96, 95% CI 0.67–1.37, p = 0.8). This remained the case when restricted to those who had attended the prevalence screen (RR = 0.93, 95% CI 0.63–1.37, p = 0.7).
These results indicate that the predicted mortality figures were accurate. There is no evidence in favour of shortening the current three-year screening interval.

O-2 Screen-detected versus symptomatic breast cancer – is improved survival due to stage migration alone?

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This aim of this study was to quantify the survival difference in screen-detected versus symptomatic breast cancer and determine whether this was due to the expected shift in the Nottingham Prognostic Index (NPI) alone.
We studied overall survival by detection mode (screen-detected or symptomatic) in 4,500 women diagnosed with invasive breast cancer in East Anglia from 1998 to 2003 with complete histopathological data on tumour size, lymph node status and grade.
In 2,602 symptomatic cases there were 417 deaths (16%) and in 1,898 screen-detected cases there were 122 deaths (6%). Cox regression analyses, after adjustment for age, showed the expected significantly lower risk of death among the screen-detected cases (RR = 0.44, 95% CI 0.35–0.54, p < 0.001). After additional adjustment for NPI, the reduction in risk was still present but markedly attenuated (RR = 0.74, 95% CI 0.59–0.91, p = 0.005). The proportion of the benefit of screen-detection explained by a shift in NPI, calculated according to the method of Freedman et al (1992, Statistics in Medicine 11, 167–178) was 63%. NPI-specific analyses suggest that the difference in survival between detection modes is most pronounced at higher NPI values (in excess of 4.4). This was confirmed by plotting 5-year survival against individual NPI values as demonstrated by Blamey et al (2007, in press, Eur J Cancer) for screen-detected and symptomatic cancers separately.
Ongoing work is attempting to further elucidate NPI-specific differences and explain the remaining 37% of the difference in survival which may be due to differences in biological or treatment variables.

O-3 Long-term results from the ZEBRA trial comparing Goserelin with CMF as adjuvant therapy in premenopausal women

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Objective: The Zoladex Early Breast cancer Research Association (ZEBRA) trial was designed to compare the efficacy and tolerability of goserelin with cyclophosphamide, methotrexate, and 5-fluorouacil (CMF) chemotherapy in pre- and perimenopausal women with node-positive, early breast cancer.
Methods: Between 1990 and 1996 a total of 1640 patients (⩽50 years of age) received goserelin (3.6 mg every 28 days for 2 years; n = 817) or CMF (6 × 28-day cycles; n = 823) for the adjuvant treatment of breast cancer. We will present an updated analysis of disease-free survival (DFS), distant disease-free survival (DDFS) and overall survival (OS) with a median follow-up of about 12 years. The data given below are preliminary.
Results: An intial analysis showed a highly significant interaction between treatment and oestrogen receptor (ER) status (p = 0.0016) and results are therefore shown by ER status. In patients with ER-positive tumours (n = 1189) goserelin continued to be equivalent to CMF for DFS (hazard ratio [HR] 1.06; 95% confidence interval [CI] 0.91, 1.24) and OS (HR 0.99; 95% CI 0.82, 1.20) and was found to be nearly equivalent for DDFS (HR 1.08; 95% CI 0.92, 1.27).

In patients with ER-negative disease (n = 304) goserelin was inferior to CMF for DFS (HR 1.61; 95% CI 1.20, 2.16) and the other two outcomes. With regard to overall safety, as reported previously, goserelin was well tolerated.
Conclusions: This follow-up analysis confirms the previously reported results from the ZEBRA trial and thus demonstrates that goserelin offers a well-tolerated effective alternative to CMF chemotherapy in the management of patients with ER-positive, node-positive early breast cancer.

O-4 Ovarian suppression (OS) and tamoxifen (TAM) as an alternative to chemotherapy in early breast cancer. Long-term results of the GROCTA02 trial

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Background: We have previously reported that comparable results can be achieved by 5 years of TAM combined with ovarian suppression or chemotherapy in pre-perimenopausal breast cancer patients affected by early breast cancer (JCO 18:2718–27, 2000). Here we report the updated results of this trial at a median follow-up time of 12 years.
Methods: Details have been published previously. In summary 124 women have been randomly assigned to receive TAM for 5 years in combination with some form of OS (most patients were given Goserelin injections for 2 yrs, but a few of them were restarded on Goserelin for one additional year when menses were restored) while 120 were given 6 cycles of "classical" (i.e. cyclophosphamide 100 mg/m^2 by mouth dd 1–14, every 4 weeks) CMF. In both groups, most of the patients were node positive (though about 15% of patients in each group were "high risk" node-negative) and all of them had ER positive tumours.
Results: At the time of the present analysis, in all 109 pts relapsed and 64 died. There was no statistically significant difference between groups either in progression-free or in overall survival (p = 0.7 for both comparisons). The comparability of results is confirmed by multivariate analysis (table below) which in addition shows that No of involved nodes and tumor grade are both independent predictors of recurrence and mortality risks.

	Recurrence			Death		
	HR	(95% CI)	P	HR	(95% CI)	P
Treatment						
CMF	1.0		0.8	1.0		0.8
TAM+OS	0.95	(0.64–1.40)		1.06	(0.64–1.77)	
Age						
⩽40 years	1.0		0.015	1.0	0.2	
>40 years	0.56	(0.35–0.89)		0.66	(0.36–1.21)	
Tumour size						
⩽2 cm	1.0		0.2	1.0		0.03
>2 cm	1.26	(0.85–1.86)		1.78	(1.05–3.01)	
No. of involved nodes						
0–3	1.0		0.002	1.0		0.055
>3	1.89	(1.27–2.84)		1.67	(0.99–2.81)	
Tumour grade						
G1–G2–Gx	1.0		0.02	1.0		0.015
G3–Gu	1.67	(1.07–2.59)		1.99	(1.15–3.44)	

Outcome analysis by prognostic strata confirms that comparable results were achieved by TAM plus OS or CMF, except in patients affected by undifferentiated tumors where both recurrence-free and mortality trends favoured those assigned to CMF (the difference in respect to mortality risk being statistically significant: p = 0.02)

Conclusions: The updated results of GROCTA 2 trial confirm that, even after a long follow-up, OS and TAM is an effective alternative treatment for ER positive breast cancer patients, irrespective of nodal status, though CT appears to be more appropriate to manage the women with less differentiated tumours.

O-5 Carcinoembryonic antigen cell adhesion molecule (CEACAM6) predicts breast cancer recurrence following adjuvant tamoxifen

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Tamoxifen has been the principal endocrine therapy for ERα-positive breast cancer patients and still remains the therapy of choice in the pre-menopausal setting. However, resistance and recurrence remain a serious problem. Our previous work has indicated that CEACAM6 was significantly up-regulated in tamoxifen-resistant (TAMr) MCF-7 derivatives compared to sensitive controls. The aim of this study was to determine the functional role of CEACAM6 in endocrine resistant breast cancer and to retrospectively test whether it was predictive of resistance in a large cohort of breast cancers with long term follow up. Up-regulation of CEACAM6 mRNA and protein in TAMr MCF-7 was confirmed by qRT-PCR and Western blotting. SiRNA-mediated silencing of CEACAM6 reduced clonogenicity of TAMr cells by ~3-fold ($p < 0.05$), and reduced anchorage-independent colony formation by ~10-fold ($p < 0.05$). Importantly, silencing of CEACAM6 partially restored sensitivity of TAMr cells to 4-Hydroxytamoxifen and restored their ability to proliferate in response to 17β-estradiol. CEACAM6 immunohistochemistry was performed on a tissue microarray comprising 108 relapsed primary human breast cancers and 243 tamoxifen-sensitive controls. Cytoplasmic and membranous staining was scored, with a maximum score of 3 indicating strong staining in >10% of cells. 57/108 (53%) of the relapsed group demonstrated strong to moderate CEACAM6 staining, which was significantly more than the non-relapsed group (76/243 (31.3%) OR = 2.46, 95% CI 1.54 to 3.91, $p < 0.0001$). In conclusion, our *in vitro* and clinical data support an important role for CEACAM6 in endocrine resistance and breast cancer recurrence.

O-6 Three years of the Breast Cancer Clinical Outcome Measures (BCCOM) project

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Data on over 45,700 primary symptomatic breast cancers diagnosed in 2002, 2003 and 2004 have been collected in the first three years of the project, including data on 374 male breast cancers. Each year, an average of 20,000 cases was sent to more than 200 UK consultant surgeons for checking.
In the absence of robust performance indicators, a set of measures has been developed by the BCCOM Project Steering Group. For example "the number and proportion of histologically node negative cancers for which more than seven nodes were harvested". BCCOM data indicate that 62% of invasive cases had known nodal status and that 52% were node negative. 59% (7,983 cases) of the node negative cancers had more than 7 nodes harvested. 46% of