

Results: Lymphocyte count declines with successive cycles of accelerated (mean: baseline=2.2; final cycle=1.3, $p<0.001$) and conventional E-CMF (mean: baseline=2.0; final cycle=1.2, $p<0.001$). Mean decline did not differ significantly by E-CMF schedule.

Table: Highest grade lymphopenia per patient

	CTCAE (v3)		
	G2 ($<0.8 \times 10^9/L$)	G3 ($<0.5 \times 10^9/L$)	G4 ($<0.2 \times 10^9/L$)
Schedule A	7/21 (33%)	5/21 (23%)	0/21 (0%)
Schedule B	9/19 (47%)	4/19 (21%)	0/19 (0%)
Conventional E-CMF	9/40 (22%)	0/40 (0%)	0/40 (0%)

Weekly blood counts Day 1 only.

Conclusion: E-CMF is associated with progressive lymphopenia irrespective of schedule, the lymphopenia observed is modest compared to accAC-P.

O-97 Attitudes towards neoadjuvant endocrine therapy and breast conserving surgery (BCS) in the elderly

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Introduction: There is little published information about the views of women aged over 70 with breast cancer regarding attitudes towards neoadjuvant endocrine treatment and breast conservation and factors that influence their choice of surgery.

Methods: A questionnaire was sent to 180 patients who were aged 70 or over when they had breast cancer surgery (122 mastectomy; 58 BCS). Responses were received from 111 (62%). Of these, 71 patients had a mastectomy (64%) and 40 had BCS (36%).

Results: 50% of patients who had mastectomy said they would have taken neoadjuvant endocrine therapy to facilitate BCS. 46% of them said that the possibility of local recurrence following BCS influenced their decision. Only 20% of patients felt that having to travel a long distance to attend for post operative radiotherapy put them off BCS. Nearly half the patients in both groups said that they were worried about the cosmetic and psychological effects of a mastectomy when they were told they had breast cancer. 98% of patients who had BCS said they were happy with their decision. Of these, 70% were happy/very happy with the cosmetic outcome.

Conclusions: Elderly patients with breast cancer are interested in considering breast conservation and half would be willing to take neoadjuvant endocrine therapy to facilitate this. Few patients are deterred by post-operative radiotherapy.

O-98 Role of the chemokine receptor CXCR4 in breast cancer metastasis

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Breast cancer cells express the chemokine (chemotactic cytokine) receptor CXCR4. There is compelling evidence that CXCR4 is a key mediator of breast cancer progression. Binding of the chemokine CXCL12 to this receptor stimulate cells to migrate out of the vasculature and establish metastasis. We aim to assess the metastatic potential of breast cancer cells by altering its expression of CXCR4.

LMD-MB-231, a low CXCR4 expressing rederived sub-line of the human breast cancer cell line MDA-MB-231, was transfected with CXCR4 by electroporation. Functional assessment of the receptor was performed with calcium

flux and chemotaxis assays towards CXCL12. An *in vivo* model was used to evaluate the metastatic potential of the transfected cells (transfectants) compared to the wild type cells. 200,000 cancer cells of either type was injected intravenously into 2 groups of SCID mice ($n=5$ each). On day 28, the mice were examined microscopically to assess tumour load in the lungs and liver.

Flow cytometry confirmed increased expression of CXCR4 on the stable transfectants. At 50 nM concentration of CXCL12, the transfectants fluxed calcium and demonstrated migration (chemotactic index 1.5) towards the chemokine. *In vivo*, the group injected with the transfectants initially demonstrated increased number of metastasis (haematoxylin and eosin staining). However, cytokeratin (epithelial cell marker) staining did not show any significant difference in metastasis.

We believe the basal levels of CXCR4 in the wild type cells may be enough to cause metastasis. We are now attempting to down-regulate this basal CXCR4 expression and will compare metastasis between the up-regulated and down-regulated cells *in vivo*.

O-99 The mTOR (mammalian target of rapamycin) inhibitor RAD001 (Everolimus) is safe and reduces proliferation in postmenopausal women with breast cancer

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Background: mTOR plays a key role in tumour cell cycle proliferation and survival. RAD001 (everolimus) is a rapamycin derivative that inhibits mTOR and its downstream substrates. This study explored, *in vivo*, RAD001 action in breast cancer.

Methods: 30 post-menopausal women with early breast cancer were given 5 mg RAD001 once daily for 14 days prior to surgery. Biopsies were taken at diagnosis and at surgery (post 14 days of treatment) and assessed for changes in proliferation (Ki67), pAkt (s473), pS6k (s235/236 and s240/244), p-mTOR, ER, and PgR.

Results: Five patients withdrew during the two week treatment period due to adverse events. All adverse events were grade 1 or 2 on the NCIC-CTC scale.

RAD001 treatment significantly decreased proliferation (Ki67, $p=0.024$). p-Akt was reduced in cases with high pre p-Akt scores but increased in patients with low pre pAkt scores. Pre p-Akt correlated significantly with reduction in proliferation (Ki67, $p=0.001$; Pearson's correlation coefficient 0.688). p-S6k staining was reduced independently of Ki67.

Discussion: RAD001 is safe and tolerable in post-menopausal early breast cancer patients. RAD001 inhibits the mTOR pathway and its downstream effectors, and significantly reduces tumour cell proliferation. High levels of p-Akt at diagnosis correlate with greater reductions in proliferation suggesting p-Akt activation as a predictive marker of mTOR activation and therefore RAD001 efficacy.

O-100 A brief review of the dermatological and gastro-intestinal toxicities of Lapatinib

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Background: Lapatinib is a dual (ErbB-1 and ErbB-2) receptor tyrosine kinase inhibitor recently approved by FDA for Her2 positive metastatic breast cancer (MBC) patients (pts) pre-treated with anthracycline/taxane/trastuzumab

containing regimes. Major concerns for lapatinib treatment are skin and gastro-intestinal toxicities (being an ErbB1 inhibitor) and cardiotoxicity (being an ErbB2 inhibitor). Cardiac events related to Lapatinib are rare and asymptomatic on meta-analyses. This review presents an analysis of lapatinib related skin (SE) and diarrhoea events (DE).

Methodology: 8 clinical trials of Lapatinib (1,126 pts) in MBC and other tumour types were analysed. Lapatinib (1000–1500 mg/day) was administered as mono-therapy (928 pts) or combination therapy (with tamoxifen 197 pts; with capecitabine 191 pts).

Results: SEs included dermatitis (commonest; 38% incidence), drug eruptions, dry skin, pruritus, urticaria, infection and nail/hair disorders. 54% pts experienced SEs and 50% DEs. Toxicities were usually CTC grade (G) 1 (55% SE; 54% DE) or 2 (35% SE and 30% DE). None had G4 SE while only 1% had G4 DE. Rashes and diarrhoea were early onset (45% SEs between days 1–14 and 44% DEs by day 6 from treatment). There was no necessity for dose reduction in 85% of patients and only 2% required discontinuation. 72% of SEs and 89% of DEs resolved. Diarrhoea was managed in 30% with standard medication (lomotil and loperamide). Severe cases required hydration, octreotide and antibiotics.

Conclusions: Lapatinib induced skin and diarrhoeal events are mild and rarely require dose modification. Efficient clinical monitoring and standard medication is sufficient for more severe cases.

O-101 Effect of tamoxifen on serum lipid levels in women at increased risk of breast cancer

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Tamoxifen is well known for its beneficial effect in decreasing the development of breast cancer in women who are at high risk. Tamoxifen has also shown to decrease levels of total cholesterol and low-density lipids (LDL) and to increase levels of high-density lipids (HDL) and triglycerides.

In the International Breast cancer Intervention Study I (IBIS-I), 7,154 women at increased risk of breast cancer were randomised to either tamoxifen 20 mg/day or placebo for 5 years. Blood samples were taken at baseline, year 1, year 5, and year 6. Here, we investigate the effect of tamoxifen on lipid parameters in women at high risk of developing breast cancer.

After 60 months of follow-up, mean concentrations of total cholesterol and LDL were significantly decreased in tamoxifen users compared to baseline measurements (Both $P < 0.001$). In contrast, triglyceride levels were significantly increased in tamoxifen users ($P < 0.001$). After tamoxifen was ceased, all lipid parameters went back to baseline measurements. Compared to women on placebo, tamoxifen significantly decreased total cholesterol and LDL levels during active treatment. No clear effect of tamoxifen was seen for HDL levels.

Tamoxifen has clearly demonstrated a beneficial effect on reducing total cholesterol and LDL. In contrast, triglyceride levels in tamoxifen users were significantly increased compared to baseline measurements or placebo users. On the basis of our data, it appears that the beneficial effects of tamoxifen in women may not only reside in preventing breast cancer, but also reducing the risk of cardiovascular disease.

O-102 Results of a phase 2 study of the oral tyrosine kinase inhibitor (TKI): axitinib (AG-013736; AG) in combination with docetaxel (DOC) vs DOC plus placebo (PL) in first-line metastatic breast cancer (MBC)

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Background: AG is a potent TKI of VEGFR 1, 2&3. A phase 1 lead-in study identified 80 mg/m² q3wks of DOC in combination with 5 mg BID of AG as the recommended phase 2 dose. The primary objective was to determine whether the time to progression (TTP) of the AG+DOC arm is superior to that of the DOC+PL arm.

Methods: Pts with no prior chemotherapy for MBC and ≥ 12 mos from adjuvant chemotherapy (aCT), measurable disease, ECOG performance status (PS) of 0–2, and no uncontrolled brain metastases were randomly assigned (2:1) to receive treatment with either DOC+AG or DOC+PL, without prophylactic growth factor in cycle 1. Tumor measurements were performed q9wks. Pts were stratified according to estrogen receptor (ER) status, prior aCT and PS (0/1 or 2).

Results: A total of 168 pts were randomized. 92 pts had received prior aCT, 27 of whom received a prior taxane. Treatment arms were well balanced for prior adjuvant and taxane therapy. A median of 7 cycles of AG+DOC (range: 1–18) and 7 cycles of DOC+PL (range: 1–23) were administered. The most common non-hematologic all-grade adverse events observed in the AG+DOC arm included diarrhea (60%), nausea (53%), alopecia (51%), fatigue (49%), stomatitis (44%), and vomiting (40%). Grade 3/4 adverse events that were increased with AG+DOC vs DOC+PL included febrile neutropenia (16 vs 7%), fatigue (13 vs 5%), stomatitis (13 vs 2%), diarrhea (11 vs 0%), and hypertension (5 vs 2%). Other grade 3/4 hematologic toxicities were similar in both arms. The median TTP (by RECIST) was 8.2 mo with AG+DOC and 7.0 mo with DOC+PL, with a hazard ratio (AG:PL) of 0.73 (prespecified, one-sided $p = 0.052$). The overall response rate (ORR) was 40% in the AG+DOC arm and 23% in the DOC+PL arm ($p = 0.038$), with a duration of response of 6.9 and 5.3 mo respectively. In a hypothesis-generating subgroup analysis, the median TTP in patients receiving prior aCT was 9.0 mo with AG+DOC and 6.3 mo with DOC+PL, with a hazard ratio of 0.54 ($p = 0.012$). Within this stratum, ORR was 45% in the AG+DOC arm and 13% in the DOC+PL arm ($p = 0.003$).

Conclusions: The anti-angiogenic TKI AG combined with DOC (80 mg/m² q3wks) as first-line therapy for MBC has an acceptable safety profile and promising anti-tumor activity.

O-103 Validating response and toxicity predictions of the “virtual patient” in neoadjuvant and adjuvant breast cancer chemotherapy

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Introduction: Optimata Virtual Patient® (OVP) is a predictive biosimulation technology, comprising computer-implemented mathematical algorithms of physiological, pathological and pharmacological processes in a patient's body. Here we report validation of OVP accuracy in predicting chemotherapy efficacy and toxicity in breast cancer patients.

Materials & Methods: Clinical and pathological parameters were collected from 17 patients with locally-advanced breast cancer (neoadjuvant AC-Taxol therapy;