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: Laptinib 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/m^2 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 $\geqslant$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/m^2 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;

Soroka), and 33 patients with liver, lung and lymph node metastases (doxorubicin or docetaxel; Nottingham). The population/drug-calibrated OVP was simulated, inputting each patient's initial data to predict individual disease course and hematopoietic toxicity under the given regimen. OVP prediction accuracy was calculated, blinding being ensured between data collection and simulations.
Results: average OVP prediction accuracy of the actual response in individual patients was 85%±9% and 70±5% in the Soroka and the Nottingham arms, respectively. Toxicity predictions were ranging from excellent to poor, as evaluated by success in recovery of neutrophil counts and day of nadir. In general, we could prove a good retrieval of day and counts of nadir as well as neutrophil peak levels in about 50% of patients whose counts were recorded frequently enough. Full statistical analysis is yet to be performed.
Conclusions: OVP showed a good accuracy in predicting response and toxicity of primary and metastatic breast cancer to AC-Taxol, doxorubicin and docetaxel chemotherapy. However, the poor efficacy prediction for some patients suggests need to evaluate new response biomarkers, as well as patients' pharmacokinetics variations.

O-104 Gene expression profiling of axillary node negative tumour tissues using microarrays to inform prognosis in breast cancer

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Traditional histopathological prognostic methods fail to accurately predict outcomes in early stage breast cancer. Several studies have used gene expression profiling to more accurately predict outcomes in breast cancer. The aim of this study was to analyse gene expression in breast tumours using microarrays and validate these results using quantitative real-time PCR (RQ-PCR).
Tissue from ten axillary-node-negative breast cancer patients with recurrence within five years were selected and matched for age, stage and treatment with 10 patients with no recurrence on long-term follow-up. Whole genome profiling was performed using the Applied Biosystems 1700 whole genome microarray. Seven genes, previously associated with outcome, were selected for further interrogation using quantitative real time PCR (RQ-PCR) in the same group of patients in order to validate the results of the microarray. RQ-PCR was performed using TaqMan chemistries and the ABI Prism 7000. Quantile-normalised intensities were used to calculate fold-changes in gene expression between prognostic groups. Associations between microarray fold-change and gene relative quantity following RQ-PCR analysis were analysed in multiple targets using Pearsons correlation coefficient (SPSS v.14).
Comparison of microarray and RQ-PCR confirmed associations between fold-changes for the different groups. Of the seven genes, GATA3 was over-expressed in good prognosis patients relative to poor prognosis ($p < 0.001$). In poor-prognosis patients GATA3 was over-expressed in ER-positive relative to ER-negative patients ($p < 0.01$).
Using this validated microarray data we have identified GATA3, which is associated with prognosis in breast cancer, further supporting a role for this transcription factor in breast cancer and hormone-regulation of this disease.

O-105 erbB Signalling in breast cancer

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Much interest has focused recently on the Epidermal Growth Factor Receptor (erbB) family, on the prognostic and predictive power of its members, their role in carcinogenesis and erbB directed therapies.
Early work has demonstrated that erbB plays a role in defining molecular subtypes. However, these data are restricted to only the erbB receptors (EGFR, HER-2, HER-3 and HER-4). No data exists on the entire family of receptors and ligands and clustering patterns which may exist in vivo.
Method: Using immunohistochemistry, we studied the combined protein expression profiles of 800 cases of primary operable breast cancers using a large panel of well characterized biomarkers for the erbB family. For each panel, the Pharm Dx® and the HercepTest antibodies was best linked to survival for EGFR and HER-2 respectively.
On the basis of these expression profiles tumours were stratified using hierarchical clustering algorithms into 5 groups. This tool reordered tumour samples into clusters with distinct patterns of protein expression. The clusters are displayed in a dendrogram in which tumours with the greatest similarity cluster together. Further analysis was performed using multiple layer perceptron (MLP)-Artificial Neural Network (ANN).
Results: Clustering showed broad similarity with previous studies based on cDNA and protein microarray. However, for the first time subcellular clustering of ligand and downstream signalling molecules were demonstrated.
The 5 clusters identified were – (1) HER-2, HER-3 and phosphoMAPK, (2) NRG3, TGF-α and EGF, (3) Hb-EGF, betacellulin, amphiregulin, NRG1β, NRG 2β, (4) NRG 1α and NRG 4 and (5) EGFR, HER-4, NRG 2α and PTEN. Groups 1, 2 and 5 had significant prognostic significance.

O-106 Preoperative ultrasound and fine-needle aspiration cytology for axillary staging in breast cancer

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Assessment of axillary lymph nodes is very important in patients with breast cancer. Axillary staging is traditionally performed by means of axillary node dissection. But now, it is more important to determine preoperative axillary nodal status. Ultrasonography (US) is the most useful method. The ultrasound-guided fine-needle aspiration cytology(US-FNAC), which is easy to access to suspicious-appearing lymph nodes, provides additional advantages to this modality. The purpose of this study was to assess the accuracy of US and US-FNAC in the preoperative diagnosis of metastatic invasion of the axilla in patients with breast carcinoma. Between May 2005 and April 2006, axillary US was performed in 189 patients with breast cancer and in 84 patients US-FNAC was done. Lymph nodes were classified as benign, suspicious, or malignant. US-FNAC was performed on lymph nodes sonographically suspicious/malignant or bigger than 1.0 cm. US-FNAC established axillary metastases in 29 of the 189 patients. These 29 were 48% of the 61 patients proven to have axillary metastases in final histology. The sensitivity, specificity, positive and negative predictive value of US alone were 54, 91, 75 and 81%, while in US-FNAC, the respective values were 82, 96, 97 and 81%. Preoperative axillary US in a combination with US-FNAC