significantly different: grade 3/4 toxicities were more pronounced in CD arm; diarrhea (GD = 8%; CD = 18%; p = 0.0088), mucositis (GD = 4%; CD = 15%; p = 0.0008), and hand-foot syndrome (GD = 0%; CD = 26%; p < 0.0001). 13% of pts stopped therapy due to adverse event on GD vs 30% on CD. Best overall response rates in both arms were 32% (p = 0.93). Median PFS (1% of patients censored in GD and 7% in CD) was 8.05 months (95% CI 6.60–8.71) in GD arm, and 7.98 (95% CI 6.93–8.77) in CD arm (log-rank p = 0.121). Of notice when interpreting this data, 11% in GD arm vs 26% in CD arm received additional chemotherapy before progression. With a median follow-up of 19.2 months, and 23% of patients censored, the median overall survival was 19.29 months (95% CI 15.57–23.59) on GD arm, and 21. 45 (95% CI 17.12–24.94) on CD arm (log-rank p = 0.982).
Conclusion: These data suggest that the two regimens are comparable in efficacy; however a more favorable toxicity profile on GD arm may be a determining factor in selecting a better treatment option. Exploratory sub-group efficacy analysis results will be presented at the meeting.

O-50 Role of Caveolin-1 expression in docetaxel resistance in breast cancer cells

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Docetaxel is very effective in the treatment of breast cancer. However, despite its efficacy, resistance to docetaxel remains a significant problem and the genetic pathways involved in docetaxel resistance are not well understood. We have previously used comparative genomic hybridization (CGH) and bacterial artificial chromosome (BAC) fine-mapping on docetaxel resistant breast cancer cell lines to identify and accurately map the minimal chromosomal regions that are modified in docetaxel-resistant cells relative to their parental docetaxel-sensitive cells. Caveolin-1 is one of the candidate genes identified by CGH and BAC-mapping to be amplified in docetaxel-resistant MDA-MB-231 cells. The role of caveolin-1 in docetaxel resistance was investigated by modulating its expression in these cells.
Caveolin-1 protein expression in docetaxel-resistant cells relative to parental, docetaxel-sensitive cells was analysed by western blot analysis. Caveolin-1 siRNA or scrambled control siRNA was transfected into docetaxel-resistant cells and mRNA knockdown was monitored by RT-PCR. MTT cytotoxicity assay was used to monitor effects on docetaxel resistance in the transfected cells.
Caveolin-1 protein expression in docetaxel-resistant cells was found to be increased 5.96-fold ($\pm$1.63) relative to docetaxel-sensitive cells. Complete knockdown of caveolin-1 mRNA expression was achieved in docetaxel-resistant cells transfected with caveolin-1 siRNA compared to scrambled control siRNA, 48 hours post-transfection. Pilot data from MTT assays demonstrated an increase in sensitivity in caveolin-1 siRNA transfected cells compared with control siRNA transfected cells, at lower concentrations of docetaxel
This preliminary study highlights that overexpression of caveolin-1 may be involved in resistance to lower concentrations of docetaxel in MDA-MB-231 breast cancer cells.

O-51 Expression of thioredoxin system proteins in locally advanced breast cancer – correlations with response to anthracycline based chemotherapy (C/T).

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The thioredoxin (Trx) system helps maintain a reducing environment in cells and regulates many key biologic processes including cellular growth, transcription factor activity, acting as an antioxidant and regulator of apoptosis. Expression of thioredoxin binding protein (TXNIP), a negative regulator of Trx, is frequently lost in tumor tissues and cell lines. Thioredoxin over expression is associated with resistance to several chemotherapeutic agents *in vitro*.
The present study examined, in 60 locally advanced breast cancer patients treated by FEC/FAC for 4–6 cycles in the neoadjuvant setting, whether the expression of Trx and related proteins (TXNIP and thioredoxin reductase, TrxR) were associated with resistance to C/T. Standard immunohistochemical techniques were used to assess protein expression both pre- and post C/T and results correlated with clinical response.
Tumours with high pre-C/T Trx and TrxR expression showed a lower complete response rate (CRR) than those with low expression ($P < 0.05$). High expression of TXNIP also correlated with a higher CRR. Trx expression significantly increased after anthracycline therapy (24.5% increase; $P < 0.001$). There was no significant increased expression of either TrxR or TXNIP following C/T. Tumors with high Trx expression showed significantly lower TXNIP expression and vice versa. We conclude that Trx and TXNIP may be clinically useful biomarkers for predicting response to anthracycline based C/T and that if using Trx expression to monitor response then TXNIP should also be assessed.

O-52 The basal phenotype (BP) is highly expressed in locally advanced breast cancer (LAPC) but does not predict response to neo-adjuvant anthracycline based chemotherapy

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Background: The prognostic value of BP is well established. This study aimed to investigate the incidence of BP in LAPC and evaluate it as a marker for predicting response to neo-adjuvant anthracycline based chemotherapy.
Methodology: The study involved 60 LAPC patients at Nottingham City Hospital treated with 6 cycles of FEC/FAC neo-adjuvant chemotherapy between December 1996 and January 2007. A pragmatic definition of BP as immunophenotypic evidence of basal cytokeratins CK5/6 and/or CK14 expression was used. Standard immunohistochemical techniques were employed to assess marker expression in pre-chemotherapy core biopsies and results correlated with clinical response (RECIST).
Results: Of 60 cores stained, 34 (56%) were BP positive. 20 of them were also ER negative (33% overall). The BP positive subgroup (34/60) responded as follows: 30 responders (88%) (15 CR and 15 PR) versus 4 non-responders (12%) (3 SD and 1 PD). In the BP negative subgroup (26/60), there were 22 responders (84%) (10 CR and 12 PR) versus 4 non-responders (16%) (3 SD and 1 PD). 14 of the 60 (23%) patients suffered recurrences: 10 (71%) were BP positive while 4 (29%) were negative. Of other response predictors such as Her2/Topo2α, Ki67 and p53, only Ki67 negativity predicted resistance in this cohort (p = 0.007).

The predictive value of BP for chemotherapy response in advanced breast cancer is currently being assessed.
Conclusions: The study demonstrates that BP is highly expressed in LAPC. However, it does not predict for response to neo-adjuvant anthracycline chemotherapy.

O-53 Biomarkers predicting response to a novel oral taxane DJ-927 in metastatic breast cancer (MBC)

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Background: DJ-927 is a novel oral taxane, whose *in vitro* tumour sensitivity is independent of p-glycoprotein (pgp) expression. Our phase 2 study in anthracycline pre-treated MBC patients showed that DJ-927 was well tolerated (response rate: 21.2%) [ESMO 06 #411P]. This single-centre analysis of 18 patients treated in the mentioned study aimed to investigate biomarkers of sensitivity to DJ-927 and assess cross-resistance to docetaxel.
Methodology: 18 patients received oral DJ-927, 27 or 35 mg/m^2, 3 weekly. 10 subsequently received single agent docetaxel. Primary tumour biopsies (n = 17, 1 unavailable) were studied for pgp, thioredoxin (Trx-1), thioredoxin reductase (TrxR1), Ki67, p53, Bcl2, VEGF, Her2, ER and progesterone expression by immunohistochemistry and correlated to response (RECIST).
Results: Best response (investigator assessed) to DJ-927 was: 7 PR (39%); 7 SD (39%) and 4 PD (22%). Response to subsequent docetaxel was: 4 PR (40%); 3 SD (30%) and 3 PD (30%). ER, Her2, vascular invasion, grade or histology did not predict for sensitivity to DJ-927. DJ-927 response was independent of pgp, Trx1, TrxR1, Ki67 and Bcl2. However, all 4 patients with PD on DJ-927 had high nuclear p53, inferring that p53 may predict DJ-927 resistance ($p = 0.015$, Fisher's exact test). Patients who had PR/SD to docetaxel following progression on DJ-927 had high pgp (5/7) and high Trx1 (6/7) levels, known docetaxel resistance markers. This raises the possibility of biomarker modulation by DJ-927.
Conclusion: Clinical sensitivity to DJ-927 appears to be independent of pgp (as *in vitro*) or Trx1/TrxR1. On progression, tumour response to docetaxel was high.

O-54 Switching to an aromatase inhibitor provides mortality benefit in early breast-carcinoma: Pooled analysis of 2 consecutive trials

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Background: The superiority of new generation aromatase inhibitors over tamoxifen in the adjuvant treatment of early breast carcinoma has emerged from several randomized trials. However, until now, only a couple trials (both ones implying early switching to an aromatase inhibitor: the ARNO 95 and the IES trials) have shown a moderate mortality benefit.
Methods: A pooled analysis of 2 prospective multicentric trials, sharing the same study design and nearly identical inclusion criteria, was performed. In both trials, women treated previously with tamoxifen for 2 or 3 years were randomly assigned to either continuing tamoxifen for an additional 2 or 3 years or to having their treatment switched to aminoglutethimide or anastrozole for a comparable time period. Mortality was analyzed according to allocated treatment and other patient and tumor variables. **Results:** In all, 828 postmenopausal women, mostly with estrogen receptor (ER)-positive and node-positive tumors who had been monitored for a median time of 78 months (range, 6–141 months) were analyzed. Of these women, 415 were randomly selected to continue tamoxifen and 413 switched to aminoglutethimide or anastrozole. All-cause mortality and breast cancer-specific mortality were significantly improved by the switch: all-cause-mortality:hazard ratio (HR) = 0.61 (0.42–0.88) $P = 0.007$; breast cancer-specific mortality: HR = 0.61 (0.39–0.94) $P = 0.025$. No increase was recorded in breast cancer-unrelated mortality in women after switching. Multivariate analysis showed that patient age, tumor size, allocated treatment, and nodal status, in that order, were independent mortality predictors.
Conclusions: Switching to an aromatase inhibitor after 2 or 3 years of tamoxifen therapy significantly improves survival compared with continuing 2 or 3 years of additional tamoxifen treatment. These findings fit in with those of a previous metanalysis including the three anastrozole switching trials (Lancet Oncol., 2006, 7: 991–996) and reinforce the indication of early switching to an aromatase inhibitor in women presently receiving adjuvant treatment with tamoxifen.

O-55 Assessment of Her-2 status using a panel of antibodies and FISH

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HER-2 expression in breast cancer has been shown to be of immense clinical importance since the realization that biologically targeted therapies to its transmembrane receptor tyrosine kinases is efficacious in prolonging disease free survival and overall survival not only in the metastatic setting but also for primary operable breast cancer. However, the optimal, most accurate and cost-effective strategy/assay to assess HER-2 status remains elusive.
We have examined HER-2 status using a panel of HER-2 antibodies [Herceptest, A0485, CBE356, and activated HER-2] and fluorescence in-situ hybridisation (FISH) in a large dataset of 800 cases. Staining was mainly membranous with cytoplasmic components ignored for this study. Overall there was good concordance with all antibodies, with HER-2 positive cases seen in 12.4% to 14.4% depending on antibody used. Using the Herceptest antibody as the true population prevalence of HER-2 expression, the best correlation with overexpression was seen with the A0485 antibody (97.8%) and the least with the activated HER-2 antibody. All antibodies showed excellent PPV (>97%) and NPV (>96%).
For borderline cases (2+), this was the least correlation amongst the assays. FISH detected HER-2 gene amplification correlated best with the Herceptest assay with 14.1% of borderline cases being amplified. When negative for FISH, all antibodies correlated excellently. This was also reflected in cases showing overexpression by immunocytochemistry. There were only few cases of unamplified HER-2 which were positive by immunoreactivity.
HER-2 positive disease showed a strong correlation with poor prognostic features. This finding translated to a worsened overall survival and shortened disease free survival. Multivariate analysis showed HER-2 status to be a marker of independent prognostic significance.