fibroblasts affect mammary epithelial cells using a coculture cell model. Benign (HB2) and malignant (MCF7) cells were stably transfected with a GFP expression plasmid, to enable subsequent differentiation from mammary fibroblasts in a coculture model, using flow cytometry. Cell proliferation was compared between epithelial and fibroblast cocultures when grown alone or in coculture using an endothelial cell line as a control. Malignant epithelial cell proliferation was enhanced by coculture with primary mammary fibroblasts, whereas benign epithelial cells showed dramatic proliferative inhibition. Two separate experiments were performed using each cell type and statistically significant p values were obtained: HB2 $p = 0.05$, $p < 0.001$; MCF7 $p = 0.001$, $p = 0.019$. The endothelial cocultures inhibited both mammary epithelial cell lines to a similar degree, suggesting that this was a mammary-specific event. Fibroblasts expressed multiple isoforms of ER beta by RT-PCR; additionally ER beta1 and beta2 were detected using Western blotting. Using a specific ER beta agonist (DPN) we noted changes in fibroblast proliferation and migration in response to wound healing and this is currently being extended to our coculture model using siRNA to knockdown ER beta. In conclusion, fibroblasts exert differential proliferative effects on mammary epithelial cells determined by their tumourigenicity and this may be mediated by ERbeta.

O-37 Fulvestrant versus exemestane following prior non-steroidal aromatase inhibitor therapy: efficacy and tolerability results from effect

J.F.R. Robertson*, on behalf of the EFECT trial investigators. *Nottingham City Hospital, UK*

Background: Non-steroidal aromatase inhibitors (AIs; anastrozole and letrozole) are increasingly used as adjuvant and first-line advanced treatments for postmenopausal women with hormone receptor-positive (HR+) breast cancer. As many patients subsequently progress, it is important to identify agents with efficacy after non-steroidal AI failure.
Methods: EFECT is a randomised, double-blind, double-dummy, multicentre, Phase III trial comparing the efficacy and tolerability of fulvestrant (Faslodex®) vs exemestane (Aromasin®) in postmenopausal women with HR+ advanced breast cancer (ABC) progressing/recurring after prior non-steroidal AI therapy. Fulvestrant loading-dose (LD) regimen was used: 500 mg on Day 0, 250 mg on Days 14, 28, and 250 mg every 28±3 days thereafter. Exemestane 25 mg was given once daily. Treatment continued until progression, death or withdrawal.
Results: 693 women were randomised to fulvestrant ($n = 351$) or exemestane ($n = 342$). ~60% of patients had received $\geqslant 2$ prior endocrine therapies and ~60% had visceral involvement. Median time to progression was 3.7 months in both groups (hazard ratio: 0.963; 95% confidence intervals: 0.819, 1.133; $p = 0.6531$). Objective response and clinical benefit rates (CBR) were also similar between groups. Median duration of response was 13.5 months vs 9.8 months for fulvestrant and exemestane, respectively. Fulvestrant and exemestane had good activity in patients with visceral disease (CBR 29.1% vs 27.2%, respectively). Both treatments were well-tolerated, with no significant differences in the incidence of pre-specified adverse events (weight gain, increased appetite, hot flushes, joint disorders, nausea/vomiting, diarrhoea, androgenic effects, injection-site reactions). Steady state plasma levels were reached within 1 month with the LD fulvestrant regimen.
Conclusions: Fulvestrant LD offers an effective and well-tolerated treatment option for postmenopausal women with ABC (including those with visceral disease) who progress/recur on non-steroidal AI therapy.

O-38 Influence of a basal phenotype on the metastatic pattern of breast cancer

A.A. Luck*, A.J. Evans, A.R. Green, E.A. Rakha, C. Paish, I.O. Ellis. *Nottingham City Hospital, UK*

Purpose: To assess whether basal phenotype (BP) influences metastatic pattern and survival in patients with metastatic breast cancer.
Materials and Methods: The BP status of a well-characterised series of consecutive primary operable breast cancers (1800 cases) was ascertained using basal CK5/6 and CK14. Follow-up data including time, site and pattern of distant metastasis and post-metastasis survival were available for 113 women with BP cancers and those were compared with 178 matching cases from women in the non-BP (NBP) group.
Results: Patients with the BP were more likely to present with intrapulmonary (25/48, [52%] BP vs. 15/64, [23%] NBP; $p = 0.0009$) and/or brain metastases (20/113, [18%] BP vs. 3/178, [2%] NBP; $p < 0.0001$). Patients with NBP were more likely to present with bone metastases in the absence of visceral disease (48/102, [47%] NBP vs. 14/62, [23%] BP; $p = 0.0017$). There was no significant difference in the frequency of pleural or liver metastases between both groups. BP was also associated with a shorter median survival with metastatic disease (10.1 months vs. 25 months, $p < 0.001$). Multivariate analysis including other established prognostic variables in metastatic breast cancer shows that BP is an independent poor prognostic factor.
Conclusion: Intrapulmonary and brain metastases are seen more frequently at metastatic presentation in BP breast cancer patients, and the BP is associated with a poorer survival after metastatic presentation. Thus assessment of basal CKs may provide valuable prognostic information that may affect patients' management.

O-39 Morphological and molecular evolutionary pathways of low and high grade breast cancers and theier putative precursor lesions

T. Abdel-Fatah*, D.G. Powe, Z. Hodi, J.S. Reis-Filho, A. Lee, I. Ellis. *University of Nottingham and Institute of Cancer Research, London, UK*

In this study, further support for our proposed route of pathogenesis concerning low grade and high grade breast cancers (LGBC and HGBC) and their precursor lesions was provided using immunophenotyping of tissue microarrays containing 790 lesions for putative tumour suppressor genes, cell cycle regulators, proliferation and differentiation markers. The putative precursor lesions were compared with their matching normal gland and invasive lesions.
Results: The epithelial cells in the flat epithelial atypia, Lobular neoplasia, ADH/ low grade DCIS and the intrinsic LGBC shared a common phenotype of CK19/18/8, ER-α, Bcl-2, and Cyclin D1 positivity. The ER-α/ER-β ratio and Cyclin D1 expression increased from precursor lesions to the invasive LGBC.
Conclusion: Our findings support the concept that FEA is the committed precursor cell lesions of LGBC/ILC. These may represent a family of precursor, in situ and invasive neoplastic lesions belonging to the luminal 'A' subclass of breast cancer. Our results suggest that the committed progenitor cells (PCs) for low grade breast neoplasia are CK19/18/8 positive and exhibit ER-α mediated CCND1 and BCL2 gene expression. Alternatively, breast cancer