are partly conflicting. Accordingly this should have implications on the management of patients with metastatic disease.

Patients with receptor negative breast cancers have been demonstrated to have a better response to neoadjuvant polychemotherapy compared with patients with receptor positive disease.

Increased expression of the HER2/neu protein has been associated with a better effect of anthracycline based therapy, although this may rather be due to a co-amplification of the topoisomerase II alpha gene, which is coding for an anthracycline binding protein.

High proliferation, measured with Ki67, has been demonstrated to be associated with a poor prognosis and a higher likelihood to respond to chemotherapy.

Multigene analyses using microarray expression profiling have been used to further identify patients with oestrogen receptor alpha positive breast cancers, who have more or less benefit from adjuvant tamoxifen.

Microarray profiling has also been used to identify gene sets associated with response and resistance to neoadjuvant docetaxel therapy, respectively. A modified Sørlie model has been used in another small study to characterize the response to neoadjuvant paclitaxel followed by FAC chemotherapy. Patients with a basal subtype or HER2/neu subtype had a higher likelihood to respond to this chemotherapy than those with the luminal or normal like subtypes.

Conclusion: Recent data indicate that more detailed molecular characterisations of breast cancers may result in improved therapy predictions.

217 Invited

Predictive factors of response to endocrine therapy

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The substantial benefit and relatively low toxicity from endocrine therapy has made it important to offer all patients with potentiallly sensitive tumours an appropriate form of endocrine therapy. Until recently this most frequently involved decisions about tamoxifen therapy. By far the most predictive factor for benefit from tamoxifen is estrogen receptor (ER) but it is also important to supplement this with progesterone receptor (PgR) since the small population of patients that is ER–PgR+ shows good benfit from tamoxifen treament. Tamoxifen-treated ER+PgR+ patients have a better outcome than ER+PgR– but it is not clear whether this is because of better intrinsic prognosis, better response to tamoxifen or a combination of the two. Recent data suggest that analysis of ER transcript levels may identify a group of very low but positive ER expressors that does not benefit from tamoxifen. Data from a retrospective subgroup analysis from the ATAC trial suggest that ER+PgR– tumours show a greater differential benefit from aromatase inhibitors than from tamoxifen but this was not confirmed in a large adjuvant trial of lerozole versus tamoxifen (BIG1–98). Two neoadjuvant trials comparing tamoxifen with aromatase inhibitors indicated that the poorer response of ER+HER2+ tumours to tamoxifen did not extend to aromatase inhibitors. The small proportion of ER+ tumours that also overexpresses HER2 means that definitive answers on the comparative benefit derived from tamoxifen or aromatase inhibitors in adjuvant trials will come only from overview analyses. Many other markers are being considered for their predictive value but our inability to derive consistent results from the assesments of PgR and HER2 in clinical trials provides a warning against the early acceptance of any new apparent associations. It is possible that new end-points and new clinical approaches are required to identify predictive factors with more confidence. Short-term presurgical studies with surrogate markers of response may offer an opportunity for this.

218 Proffered Paper Oral

Stroma related gene signature predicts sensitivity to epirubicin containing neoadjuvant chemotherapy. A microarray study of 102 patients included in EORTC 10994/BIG 00–01 trial

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Background: The survival benefit of adding taxanes in the adjuvant setting remains modest and is associated with additional toxicity and cost. Biological predictive markers of sensitivity to anthracyclines would allow tailored chemotherapy treatment. Pathological complete response (pCR) is a surrogate for chemosensitivity and the goal of this study was to identify a gene expression signature predicting for a pCR following neo-adjuvant anthracycline based chemotherapy.

Methods: The tumours used were from patients in the ongoing large randomized trial (EORTC 10994/BIG 00–01), which compares an anthracycline containing regimen without taxane (FEC: fluorouracil + epirubicin + cyclophosphamide × 6) with a taxane containing regimen (docetaxel) in patients with large operable or locally advanced/inflammatory breast cancer. The study was restricted to cases meeting the following criteria: (1) non T4 tumours, (2) treated with neoadjuvant FEC chemotherapy, (3) more than 20% tumour cells on the frozen sample, (4) good quality and yield (at least 200 ng) of RNA extracted from the centrally stored frozen sample. After T7 amplification, samples were hybridized to X3P Affymetrix arrays. We used first a naïve gene selection by learning loop. Genes selected by t-test were used to create an unweighted compound covariate-based predictor. In a second approach we used 40 metagenes that capture information about physiology, pharmacology and molecular pathology. A leave 10% out cross validation was performed 100 times. Lastly we evaluated the response prediction reached with successfully mapped genes from previously published gene signatures (including the NKI 70-gene signature) using our data set as an external independent validation set.

Results: 102 patients (39 pCR) underwent a successful gene-expression array. With the naïve gene selection and 3 different stroma metagenes area under the ROC curve were 0.64, 0.62, 0.66 and 0.65 respectively. The 70-gene signature did not predict for pCR.

Discussion: This series is the largest series trying to identify a gene signature predicting for response to a specific regimen. The predictor, using both the naïve gene selection and the metagene approaches, gives better results than chance. In our series the "Affymetrix-X3P mapped 70-gene signature" has no predictive power for pathological response. Results of the response prediction of other published gene signatures will be presented at the meeting.

219 Proffered Paper Oral

Predictors of early recurrence in postmenopausal women with hormone receptor positive breast cancer in the BIG 1–98 trial

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Introduction: The BIG 1–98 trial, coordinated by the International Breast Cancer Study Group, compared letrozole (LET) to tamoxifen (TAM) given for 5 years (y) alone or in sequence, in postmenopausal women with estrogen and/or progesterone receptor (ER/PgR) positive breast cancer. Patients (pts) were randomized to either the 2-arm option (5y TAM or 5y LET) or the 4-arm option (these two arms plus 2y TAM followed by 3y LET or 2y LET followed by 3y TAM). The primary core analysis comparing LET to TAM as monotherapy showed a significant benefit of LET on disease-free survival, particularly for distant metastasis. The aim of the present analysis was to retrospectively identify clinical and pathological prognostic factors of early recurrence in women treated on the 4-arm option of BIG 1–98.

Methods: A total of 6091 eligible pts were analyzed according to the treatment to which they were randomized (91 ineligible pts were excluded). Analyses were based on treatment with TAM or LET alone. At a median follow-up of 25.0 months, 216 pts (3.5%) had an event, defined as the first proven occurrence of local recurrence in the scar (N = 8) or chest wall (N = 6) after mastectomy, local recurrence in the chest wall outside the breast after breast-conserving surgery (N = 1), or distant recurrence (N = 201). Prognostic factors tested were age at randomization, adjuvant and/or neoadjuvant chemotherapy use, pathological tumor size, ER/PgR status, node positivity, tumor grade, and mitotic grade. Logistic regression analyses were performed, and all models included treatment. Interactions between treatment and the covariates in the final model were tested individually. A significance level of alpha = 0.05 was used.

Results: The final model was based on 5980 pts and 212 events (111 pts with missing covariates were excluded). The significant prognostic factors were tumor size ($p < 0.001$), ER/PgR status ($p < 0.001$), node positivity ($p < 0.001$), and tumor grade ($p < 0.001$). There was a significant interaction between node positivity and treatment ($p = 0.003$). Pts with the greatest risk of recurrence had ⩾4 positive nodes, tumors ⩾5 cm, ER+/PgR- tumors and grade 3 tumors. The increase in risk associated with increased node positivity was greater for pts randomized to TAM than to LET.

Conclusion: These significant prognostic factors may indicate relative resistance to LET or TAM and could facilitate choice between the two treatments given alone or in sequence.