Results: Lapatinib was used as a 2nd line treatment in 77 patients, as 3rd line in 65 and as 4th or further line in 53, 14 patients received lapatinib after failure of adjuvant trastuzumab therapy. Median duration of lapatinib therapy was 20.6 weeks (range 1–146 w). Complete response was achieved in 13 patients(6.1%), partial response in 31 (14.6%), stable disease in 118 (55.4%), in 26 disease progressed (12.2%) and in 25 the response could not be assessed (11.7%). Most common toxicities were diarrhea in 11.7%, rash/skin toxicity in 10.8%, nausea/vomitus in 5.2% and hepatotoxicity in 2.3%. No cardiac toxicity was reported. Therapy was discontinued due toxicity in 9.0%. PFS (95% CI) for whole group was 7.1 months (range 5.9−8.5). Overall survival (95% CI) was 17.2 months (range 15.8–18.6), probability of 1-year OS was 64%. An analysis of lapatinib efficacyfor different lines of treatment revealed overall response rate 24.7% in 2nd line, 10.8% in 3rd, and 22.7% in 4th or further line. PFS was 7.6 months in 2nd line, 7.0 in 3rd, and 6.3 in 4th or further line. OS was 16.8 m in 2nd line, 18.8 in 3rd, and 15.7 in 4th or further lines.

Conclusion: Lapatinib in combination with capecitabine proved its efficacy in trastuzumab pretreated metastatic breast cancer. Therapy was well tolerated. Diagnosis and treatment specific registry is a useful and feasible method for cancer treatment evaluation in standard clinical practice.

189 Poster

Antitumor Effect of the MTor Inhibitor Everolimus in Combination with Trastuzumab On Human Breast Cancer Stem Cells in Vitro and in Vivo

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Background: Recent evidence has suggested that breast cancer contains a rare population of cells called cancer stem cells (CSCs), which have the ability of extensive self-renewal and contribute to metastasis and therapeutic resistance. This study evaluated the effects of an mTOR inhibitior everolimus alone or in combination with trastuzumab on stem cells sorted from HER2-overexpressing primary breast cancer cells and breast cancer cell lines (BT474) in vitro and in vivo.

Material and Methods: *In vitro* studies, we sorted $ESA^+CD44^+CD24^{-/low}$ cells as stem cells using flow cytometry from primary breast cancer cells and BT474 cell lines. MTT assays were used to quantify the inhibitory effect of the drugs on total cells and stem cells. Apoptosis and the cell cycle distributions of stem cells were examined by flow cytometry. The tumorigenicity of stem cells after treatment was investigated by soft agar colony formation assays. In vivo studies, the BALB/c mice were injected with BT474 stem cells and the different treatments were administered. After necropsy, the expression of Ki67, CD31, AKT1, and phospho-AKT (Thr308) was analyzed by immunohistochemistry.

Results: In vitro studies, compared with their total cells, there were greater resistance to the standard treatment doses of trastuzumab in cancer stem cells sorted from primary breast cancer and BT474 cells (16- and 19-fold, respectively).Treatment with everolimus resulted in growth inhibition of stem cells in a dose-dependent manner. Compared with single-agent therapy, the combination of everolimus with Trastuzumab was more effective in the inhibition of cell growth($P < 0.001$) and tumorigenicity($P < 0.001$).In addition, an increase in G1 cell cycle arrest and an increased population of cells in early apoptosis were seen in the combination treatment group compared with either single-agent group ($P < 0.01$).In vivo, the volumes of the xenograft tumors significantly decreased in everolimus alone group compared to untreated group ($P = 0.007$), and everolimus plus trastuzumab therapy was much more effective at reducing tumor volume in mice compared with either single-agent alone ($P < 0.05$). Compared with everolimus alone, the combination of everolimus and trastuzumab reduced the expression of KI-67, AKT1 and phospho-AKT (Thr308) ($P < 0.05$).

Conclusion: Everolimus has effective inhibitory effects on HER2-overexpressing stem cell in vitro and vivo. Combination treatment of everolimus and trastuzumab could inhibit the growth of HER2-overexpressing stem cells in vitro and in vivo, in addition its effect was more effective than either drug alone. Everolimus plus trastuzumab were considered to be rational combination treatments and valuable to test in human clinical trials.

190 Poster

An Audit of the Impact of New Cardiac Guidelines On Adjuvant Transtuzumab Therapy in the Northern Cancer Network

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Background: In March 2009 Jones et al published updated cardiac guidelines for the management of adverse cardiac events following the use of transtuzumab in HER-2-positive early breast cancer (EBC). These guidelines aimed to encourage a proactive and practical approach to the management of transtuzumab cardiotoxicity. These guidelines were rapidly adopted within the Northern Cancer Network in the UK. We performed a retrospective audit to assess whether the new guidelines altered the number of patients receiving and completing adjuvant transtuzumab for EBC.

Methods: Patients who had received transtuzumab for HER−2-positive EBC at Newcastle Hospitals and Wansbeck hospital in the North of England between June 2006 and June 2010 were identified from pharmacy records. Patients were split into 2 groups: those who commenced treatment before March 2009 and those after March 2009. Information was collected from patient records (electronic and paper) for demographics, changes in ejection fraction, number of cycles of transtuzumab received, delays in treatment and cardiology interventions.

Results: A total of 163 patients were identified. 108 before and 55 after March 2009. The average age of the patients and the average initial cardiac ejection fraction were similar. 93% (51) completed the full course of transtuzumab post the guidelines changing and 81% (88) prior to March 2009 ($p = 0.06$). There were less delays in treatment 5.5% versus 10%, 3 and 11 patients respectively; and fewer referrals for cardiology review 30% vs 20%, 32 and 11 patients respectively.

Conclusions: Adopting the new guidelines has allowed more women to complete their planned transtuzumab treatment and with fewer delays. Further follow-up is needed to assess whether this will have an impact on long term survival and future cardiac complications.

191 Poster

DETECT III − a Multicenter, Randomized, Phase III Study to Compare Standard Therapy Alone Versus Standard Therapy Plus Lapatinib in Patients with Initially HER2-negative Metastatic Breast Cancer and HER2-positive Circulating Tumor Cells

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Background: In breast cancer patients, HER2 status may change over the course of the disease. Approximately 20−30 % of initially HER2-negative patients have HER2-positive metastasis (Zidan 2005, Tewes 2009). Re-evaluation of HER2 status on metastatic tissue is warranted, but not always possible, especially during the course of therapy. Determining HER2 status on circulating tumor cells is one option for re-evaluating HER2 status at the time metastasis is diagnosed as described in our previous study DETECT I (Fehm 2010). However, at present it is unclear if therapy based on the HER2 status of CTC offers a clinical benefit for patients. Therefore, the study DETECT III aims to assess whether lapatinib, as one of the HER2-targeted therapies, in initially HER2-negative breast cancer patients with HER2-positive CTC is effective at the time of distant disease.

Trial Design: DETECT III is a prospective, multicenter, randomized, open-label, two arm phase III study. As only half of the patients with HER2-negative MBC will be CTC-positive and approx. 32% will exhibit HER2-positive CTCs, a screening of about 1420 patients will be needed. Approx. 228 patients will be enrolled in the study and randomized 1:1 to one of the following regimens Arm A ($n = 114$): Standard Treatment, Arm B ($n = 114$): Standard Treatment plus Lapatinib.