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.

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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.

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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.

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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.

Main eligibility criteria:
- MBC
- HER2-negative primary tumor tissue and/or HER2-negative metastatic disease
- Evidence of HER2-positive CTCs
- Indication for a standard chemo- or endocrine therapy
- ⩾ 1 lesion that can be measured according to RECIST

Objectives: The objective is to prove the clinical efficacy of lapatinib in patients with MBC who exhibit HER2-positive CTCs although the primary tumor tissue and/or biopsies from metastatic sites were investigated for HER2 status and showed HER2-negativity.

Primary endpoint:
- PFS

Secondary endpoints:
- CR and PR
- Clinical benefit rate
- Overall survival
- Dynamic of CTC
- QoL
- Safety and tolerability of lapatinib

Perspectives: The DETECT III trial has been designed to correlate the HER2 status of CTCs to the clinical response to HER2-directed therapies. It is the first study where treatment is based on phenotypic characteristics of CTCs by modern CTC-technology. If this trial succeeds in proving efficacy of lapatinib in patients with initially HER2-negative primary tumor but HER2-positive CTCs, this will establish a new strategy in the treatment of metastatic breast cancer.

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Pertuzumab and Trastuzumab in Combination with an Anthracycline-containing or an Anthracycline-free Standard Chemotherapy in the Neoadjuvant Treatment of HER2-positive Breast Cancer (TRYPHAENA)

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Background: Pertuzumab (P) is a humanised monoclonal antibody targeting HER2 at a different epitope than trastuzumab (H) and preventing HER2 dimerisation. The combination of both antibodies shows increased activity in the neoadjuvant treatment of HER2-positive breast cancer (BC). TRYPHAENA assessed cardiac safety and efficacy of H plus P and an anthracycline-containing or anthracycline-free standard chemotherapy in neoadjuvant therapy.

Materials and Methods: Patients (pts) with HER2-positive operable, locally advanced or inflammatory BC were randomised to receive H+P (cycles 1−6) with FEC (cycles 1−3) and docetaxel (T) (cycles 4−6) (Arm A), or FEC (cycles 1−3) followed by T+H+P (cycles 4−6) (Arm B), or T+H+P+carboplatin (Cb) (cycles 1−6) (Arm C). Dose: P 840 mg loading and 420 mg maintenance; H 8 mg/kg loading and 6 mg/kg maintenance; T 75 mg/m^2 escalating to 100 mg/m^2, if tolerated (not in Arm C); FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 600 mg/m^2) and Cb AUC 6, all given q3w. Primary endpoint: cardiac safety during neoadjuvant therapy evaluated by symptomatic left ventricular systolic dysfunction (LVSD) and left ventricular ejection fraction (LVEF). Key secondary endpoints: overall safety and pCR defined as absence of invasive disease in the breast at surgery, irrespective of nodal status. This trial is registered at clinicaltrials.gov, NCT00976989.

Results: From 12/2009−01/2011 225 pts were enrolled. Baseline (BL) characteristics were balanced between treatment arms: median age 50 yrs, median tumour size 45 mm, hormone receptor-negative tumours: 49% of pts, histological grade 3 disease: 35% of pts, 30% of pts were clinically node-negative. During neoadjuvant treatment, symptomatic LVSD of grade ⩾3 was reported in 0% of pts in Arm A, 2.7% in Arm B and 0% in Arm C. LVEF declines of ⩾10% points from BL to <50% were reported in 4.2% (Arm A), 5.3% (Arm B) and 3.9% (Arm C) of pts. The most common grade ⩾3 adverse events across all arms were neutropenia (45.3%), febrile neutropenia (14.8%), leukopenia (14.3%), anaemia (7.2%) and diarrhoea (7.2%). pCR rates in Arms A, B and C were: 61.6%, 57.3% and 66.2% respectively.

Conclusions: Results indicate an acceptable cardiac and overall safety profile and high pCR rates with H+P in combination with standard neoadjuvant chemotherapy. TRYPHAENA supports the ongoing APHINITY study, a Phase III trial to evaluate H+P plus standard chemotherapy in the adjuvant setting.

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Phase I Safety Experience with the Oral Pan-class I PI3K Inhibitor BKM120 in Patients with Metastatic Breast Cancer (mBC)

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Background: The recommended Phase II dose of BKM120, an oral pan-class I PI3K inhibitor, is 100 mg/d either as monotherapy or in combination. In a general cancer population, most frequent adverse events (AEs) (⩾20%) were fatigue/asthenia, decreased appetite, diarrhea, hyperglycemia, nausea, rash, and mood disorders. Safety experience with BKM120 in pts with mBC from 3 recently reported Phase I trials is summarized.

Methods: In Study 1 (NCT01068483), pts with advanced solid tumors (N = 81), received continuous BKM120 (12.5–150 mg/d; 72% at 100 mg/d); a subgroup of mBC pts is evaluated here (Study 1A; 80–150 mg/d; 90% at 100 mg/d). In Study 2 (NCT01132664), pts with HER2+ mBC resistant to trastuzumab (T)-based therapy (progression on/within 4 weeks since last T dose) received continuous BKM120 (50–100 mg/d; 71% at 100 mg/d) + the standard weekly dose of T. In Study 3 (NCT01248494), post-menopausal pts with ER+/HER2− mBC received continuous BKM120 (100 mg/d) + letrozole (2.5 mg/d); 90% had received a prior aromatase inhibitor.

Results: 58 pts with mBC were evaluable for safety in the 3 Ph I studies (see table). The AE profile in mBC appears consistent with the general cancer population in Study 1. Gr 3* AEs (⩾5%) suspected to be related to study drug are shown in the table.

Gr 3 AEs, n (%)	mBC			Advanced solid tumors
	Study 1A (BKM120) N = 20	Study 2 (BKM120 + T) N = 18†	Study 3 (BKM120 + letrozole) N = 20	Study 1 (BKM120) N = 81
Transaminase increase	4 (20)	2 (11)	3 (15)	9 (11)
Hyperglycemia*	2 (10)	2 (11)	2 (10)	3 (4)
Psychiatric disorder**	2 (10)	2 (11)	0	4 (5)
Fatigue/asthenia	2 (10)	2 (11)	1 (5)	3 (4)
Diarrhea	2 (10)	0	0	3 (4)
Anxiety	1 (5)	0	1 (5)	1 (1)
Depression	0	0	1 (5)	1 (1)
Rash	0	1 (6)	0	4 (5)
Pruritus	1 (5)	0	0	2 (3)
Hypersensitivity	0	1 (6)	0	1 (1)
Others***	3 (15)	1 (6)	0	3 (4)

*Only 2 BKM120-related Gr 4 AEs were observed: hyperglycemia at 150 mg/d (inc. 1 mBC pt).
**Affective disorder or mood alteration.
***Inc. photosensitivity reaction, cataract, colitis, abdominal pain upper, hypokalemia, restlessness †18 pts enrolled (safety set), 17 received BKM120 (full analysis set).

Preliminary assessments of BKM120 activity in mBC show that: as monotherapy (Study 1A), 2 pts had RECIST partial responses (PRs) (confirmed in 1 pt); in combination with T (Study 2), 3 pts had PRs (confirmed in 1 pt); and in combination with letrozole (Study 3), a PR was seen in 1 pt.

Conclusions: The safety profile of BKM120 in pts with mBC, either as monotherapy or in combination with T or letrozole, is acceptable and manageable. Preliminary signs of activity have been observed.