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.