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

HER2 status may change over the course of disease in breast cancer pts. Approx. 20-30% of pts with initially HER2-negative breast cancer have HER2-positive metastasis (Zidan et al. 2005; Tewes et al. 2009). Determining HER2 status on CTC is one option to re-evaluate HER2 status and to use CTCs as a liquid biopsy at the time metastasis is diagnosed. Currently it is unclear if HER2-targeted therapy based on the assessment of HER2 status of CTC reveals a clinical benefit. 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

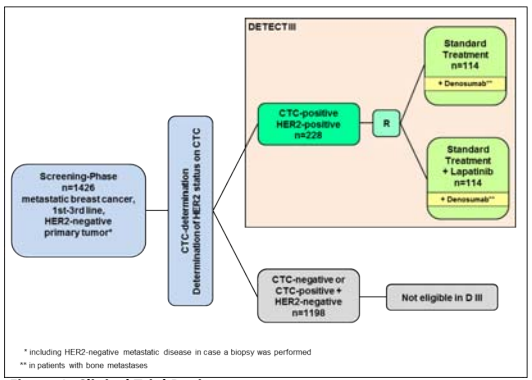

Figure 1: Clinical Trial Design

Main Eligibility Criteria

- Metastatic breast cancer
- HER2-negative primary tumor tissue and/or biopsies from metastatic sites or locoregional recurrences
- Evidence of HER2-positive CTCs
- Indication for a standard chemo- or endocrine therapy whose combination with lapatinib is either approved or has been investigated in prior clinical trials (see Table 1)
- ≥1 lesion, according to RECIST 1.1

Lapatinib + Monochemotherapy	Recommended Treatment Regimen
lapatinib + docetaxel	Daily lapatinib 1250 mg + docetaxel 75 mg/m² d1 q3w. After discontinuation of docetaxel lapatinib mono 1500 mg daily.
lapatinib + paclitaxel	Daily lapatinib 1500 mg + paclitaxel 80 mg/m²/weekly, or daily lapatinib 1500 mg + paclitaxel 175 mg/m² d1, q3w. After discontinuation of paclitaxel lapatinib mono 1500 mg daily.
lapatinib + capecitabine	Daily lapatinib 1250 mg + capecitabine 2000 mg/m² d1-14, q3w. After discontinuation of capecitabine lapatinib mono 1500 mg daily.
lapatinib + vinorelbine	Daily lapatinib 1000 mg + vinorelbine p.o. 50 mg/m² d1, 8 q3w. After discontinuation of vinorelbine lapatinib mono 1500 mg daily.
lapatinib + NPLD (non pegylated liposomal doxorubicin)	Daily lapatinib 1250 mg + NPLD 60 mg/m² d1 q3w. After discontinuation of NPLD lapatinib mono 1500 mg daily.
Lapatinib + Monoendocrine Therapy	**Recommended Treatment Regimen**
lapatinib + aromatase inhibitors	Daily lapatinib 1500 mg + AI as recommended for monotherapy

Table 1: Treatment Options within DETECT III

Specific Aims

The **objective** of the trial is to prove the clinical efficacy of lapatinib in patients with metastatic breast cancer who exhibit HER2-positive circulating tumor cells (CTC) although the primary tumor tissue and/or biopsies from metastatic sites showed HER2-negativity. **Primary endpoint** is progression free survival. **Secondary endpoints** include overall response rate, clinical benefit rate, overall survival and dynamic of CTC.

CTC - Determination

To determine CTCs and HER2-status the CellSearch®-System (Veridex, USA) is used. After immunomagnetic enrichment with an anti-Epcam-antibody, cells were labeled with anti-CK8/18/19, anti-CD45 antibodies as well as a fluorescein conjugate antibody for HER2-phenotyping. To be eligible pts must have ≥1 CTC with strong HER2-staining (+++).

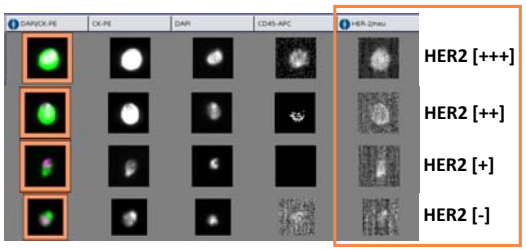

Figure 2: Screenshots of CTC-Determination

Recruitment

The Detect III-trial started recruiting in February 2012. The number of participating sites in Germany and enrolled patients are shown in table 2, updated 23rd November 2012.

Study-sites		Patients	
Overall	108	Screened	289
Open	90	Determined	269
Active	52	CTC- positive / HER2-positive	41

Table 2: Number of Participating Sites and Enrolled Patients

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 one of the first trials where treatment is based on phenotypic characteristics of CTCs by modern CTC-technology (Veridex). 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.

Acknowledgment

Deutsche Gesellschaft für Senologie · Brustkrebs Deutschland e.V. · NOGGO · GÜTESIEGEL A DER DEUTSCHEN KREBSGESELLSCHAFT · BNGO · GBG German Breast Group · mamazone · AIO · SUCCESS BIG-Member · TraFo AGO-B Breast Study Group

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