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

C. Melcher[1], W. Janni[1], B. Jäger[2], A. Schneeweiss[3], K. Pantel[4], U. Ortmann[1], E.-F. Solomayer[5], V. Müller[6], B. Rack[2], T. Fehm[7]

- on behalf of the DETECT study group -

1 Gynecology and Obstetrics, University Hospital Düsseldorf, Germany; 2 Gynecology and Obstetrics, University Hospital Munich, Germany; 3 National Center for Tumor Diseases, University Hospital Heidelberg, Germany; 4 Department of Tumor Biology, University Hospital Hamburg, Germany; 5 Gynecology and Obstetrics, University Hospital Homburg, Germany; 6 Gynecology and Obstetrics, University Hospital Hamburg-Eppendorf, Germany; 7 Gynecology and Obstetrics, University Hospital Tübingen, Germany

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 et al. 2005, Tewes et al. 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 et al. 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.

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 Fig.2)
- ≥1 lesion measurable according to RECIST

Trial Design

DETECT III is a prospective, multicenter, randomized, open-label, two arm phase III study.

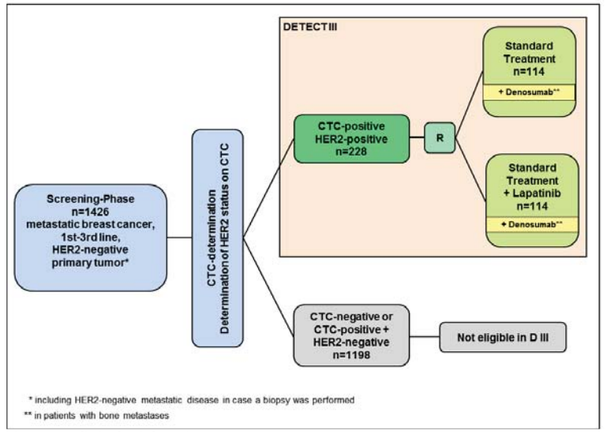

Figure 1: Clinical Trial Design

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

Figure 2: 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 were investigated for HER2 status and showed HER2-negativity.

Primary Endpoint	Secondary Endpoints
• Progression free survival	• Overall response rate • Clinical benefit rate • Overall survival • Dynamic of CTC • Quality of Life (QoL) • Safety and tolerability of lapatinib • Level of compliance to study protocol • Intensity of pain

Statistical Methods

The primary endpoint will be analyzed by Kaplan-Meier method using the logrank test in order to compare the progression-free survival distributions of the two arms.
Efficacy, toxicity and other event rates are calculated, providing confidence intervals. In case of comparison between patient groups, these rates will be analyzed by Fisher's exact test or χ^2 test, respectively.
The Kaplan Meier analysis for all event related data will be carried out overall for the whole patient population. Furthermore a Cox regression analysis will be done using the following covariates

- Hormone receptor status (positive/negative)
- Number of prior chemotherapy lines for MBC
- Prior endocrine therapy for metastatic disease
- Endocrine treatment vs. cytotoxic treatment
- One metastatic site vs. multiple metastatic sites
- Bone metastases vs. no bone involvement
- Performance status

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.

Acknowledgment

Deutsche Gesellschaft für Senologie
Brustkrebs Deutschland e.V. Prognose Leben
NOGGO e.V.
GÜTESIEGEL A DER DEUTSCHEN KREBSGESELLSCHAFT
BNGO
GBG GERMAN BREAST GROUP
mamazone
AIO
TRAFO SUCCESS
AGO-B BIG-Member BREAST STUDY GROUP

References

Zidan, J., et al., Comparison of HER-2 overexpression in primary breast cancer and metastatic sites and its effect on biological targeting therapy of metastatic disease. Br J Cancer, 2005. 93(5): p. 552-6.

Tewes, M., et al., Molecular profiling and predictive value of circulating tumor cells in patients with metastatic breast cancer: an option for monitoring response to breast cancer related therapies. Breast Cancer Res Treat, 2009. 115(3): p. 581-90.

Fehm, T., et al., HER2 status of circulating tumor cells in patients with metastatic breast cancer: a prospective, multicenter trial. Breast Cancer Res Treat, 2010. 124(2): p. 403-12.