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.

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
- Progression free survival

Secondary Endpoints
- Overall response rate
- Clinical benefit rate
- Overall survival
- Dynamic of CTC
- Quality of Life (QoL)
- 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 χ² 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

References


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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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