The DETECT Study Concept – Individualized Therapy of Metastatic Breast Cancer Based on Circulating Tumor Cells

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 (MBC) Cancer and HER2-Positive Circulating Tumor Cells

Condition
HER2-negative metastatic breast cancer
HER2-positive circulating tumor cells

ClinicalTrials.gov Identifier
NCT01619111

EudraCT Number
2010–024238–46

Study Design
Study Type: Interventional
Study Phase: III
Allocation: Randomized
Intervention Model: Two-Arm Assignment
Masking: Open-label

Primary Purpose: Treatment
Estimated Enrollment: 120 Patients

Interventions
Drug: Lapatinib
Study Arm A: Standard treatment (endocrine therapy / chemotherapy)
Study Arm B: Standard treatment + lapatinib

Primary Outcome Measure
CTC clearance rate: proportion of patients with at least one CTC detected in 7.5ml of peripheral blood drawn before treatment that show no evidence of CTCs in the blood after treatment.

Sponsor
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Description
The HER2 status in breast cancer patients may change during the course of the disease. In 30% of initially HER2-negative patients with circulating tumor cells (CTCs), HER2-positive CTCs can be detected in peripheral blood samples. At present, it is unclear if therapy based on the HER2 status of CTCs offers a clinical benefit for these patients. The DETECT III trial compares lapatinib, as HER2-targeted therapy in combination with standard therapy versus standard therapy alone in those patients, with initially HER2-negative metastatic breast cancer and HER2-positive CTCs. As one of the first interventional trials based on the assessment of CTC phenotypes, the DETECT III trial aims to evaluate the efficacy of HER2-targeted therapy in patients with metastatic breast cancer and HER2-positive CTCs as well as the significance of CTCs as an early predictive marker for treatment response.

Eligibility Criteria

Main Inclusion Criteria
• MBC which cannot be treated by surgery or radiotherapy only
• Primary tumor tissue and/or biopsies from metastatic sites must be HER2-negative
• Evidence of at least one HER2-positive CTC (extracted from 7.5ml patient blood)
• Indication for a standard chemo- or endocrine therapy
• Up to 3 chemotherapy lines for metastatic disease
• Female patients, age ≥ 18 years
• ECOG performance status ≤ 2

Main Exclusion Criteria
• Life expectancy < 3 months
• Male patients
• Pregnancy or nursing
• Primary tumor or biopsies from metastatic sites or locoregional recurrences showing HER2-positivity
• Any prior treatment with anti-HER2 directed therapy
• History of > 3 chemotherapy lines for metastatic disease
DETECT IV – a Multicenter Phase II Study in Patients with HER2-Negative Metastatic Breast Cancer and Persisting HER2-Negative Circulating Tumor Cells (CTCs)

**Condition**
HER2-negative and hormone receptor-positive metastatic breast cancer
HER2-negative circulating tumor cells

**ClinicalTrials.gov Identifier**
NCT02035813

**EudraCT Number**
2013–001269–18

**Study Design**

**Study Type:** Interventional

**Study Phase:** II

**Allocation:** Non-randomized

**Intervention Model:** Parallel Assignment

**Masking:** Open-label

**Primary Purpose:** Treatment

**Estimated Enrollment:** 400 patients (DETECT IVa) and 120 patients (DETECT IVb)

**Interventions**

**Drug:** Everolimus (DETECT IVa), eribulin (DETECT IVb)

**Study Arm A:** Everolimus + endocrine therapy

**Study Arm B:** Eribulin mono-chemotherapy

**Primary Outcome Measure**

Progression-free survival, defined as time interval from date recruitment until progressive disease or death from any cause, whichever comes first.

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**Description**

Several studies have indicated that determining prevalence and number of circulating tumor cells (CTCs) at various time points during treatment may be an effective tool for assessing treatment efficacy in metastatic breast cancer (MBC). However, even if the prognostic value of CTCs in MBC is well understood, the role of both CTC prevalence and CTC phenotype in predicting treatment response needs further investigation. DETECT IV is a prospective, multicenter, open-label, phase II study in patients with HER2-negative metastatic breast cancer and persisting HER2-negative circulating tumor cells (CTCs). Additional research on CTC dynamics and characteristics will provide a better understanding of the prognostic and predictive value of CTCs and is one step into a more personalized therapy for MBC.

**Eligibility Criteria**

**Main Inclusion Criteria**

- MBC which cannot be treated by surgery or radiotherapy only
- Primary tumor tissue and/or biopsies from metastatic sites must be HER2-negative
- Evidence of exclusively HER2-negative CTCs
- Female patients, age ≥ 18 years
- ECOG performance status ≤ 2
- For Everolimus only: Indication for an endocrine therapy
- For Everolimus only: Up to two lines of previous cytostatic treatment for MBC
- For Eribulin only: Any endocrine therapy in the history is allowed
- For Eribulin only: Postmenopausal women
- For Eribulin only: Either hormone-receptor (HR) negative MBC or HR-positive MBC with indication for chemotherapy
- For Eribulin only: Up to three previous chemotherapy treatment lines for metastatic disease

**Main Exclusion Criteria**

- Life expectancy < 3 months
- Male patients
- For Everolimus only:
  - Known hypersensitivity to everolimus or other mTOR inhibitors
- For Eribulin only:
  - Pre-existing neuropathy grade 3 or higher
  - Pregnancy or nursing
Especially for diseases that are not curable such as metastatic breast cancer (MBC), the maintenance of quality of life is one of the main aims of treatments. Adverse events are well-known side effects of any cytostatic treatment and impact the patients’ quality of life. Therefore, new treatment options are developed that should stop or at least slow down metastatic spread of cancer without causing negative side effects in terms of high-grade adverse events. For patients with hormone-receptor positive and HER2-positive MBC the combination of HER2-targeted therapy with endocrine therapy has already been proven to be an effective and in many cases valuable alternative to the combination of HER2-targeted therapy with chemotherapy. The high relevance of HER2-targeted/endocrine treatment combinations derives from the fact that potential chemotherapy-related toxicity can be avoided, which in turn positively affects quality of life. The combination of dual HER2-targeted therapy with trastuzumab and pertuzumab plus endocrine therapy might offer a better treatment option in patients with HER2-positive and hormone receptor-positive MBC. However, this combination has not been evaluated and compared to the combination of dual HER2-targeted plus chemotherapy in a prospective randomized phase III clinical trial.

### Eligibility Criteria

**Main Inclusion Criteria**
- Metastatic breast cancer which cannot be treated by surgery or radiotherapy only
- Primary tumor tissue and/or biopsies from metastatic sites must be HER2-positive
- Up to two prior chemotherapies for the metastatic disease
- Female patients, age ≥ 18 years
- ECOG performance status ≤ 2

**Main Exclusion Criteria**
- History of hypersensitivity reactions attributed to trastuzumab or pertuzumab
- Previous treatment with pertuzumab
- Life expectancy < 3 months
- History of serious cardiac disease
Circulating tumor cells (CTCs) can be detected in the peripheral blood of patients with both early and advanced breast cancer. They are involved in the processes of hematogenic dissemination and thereby the development of distant metastases [1]. The prognostic and predictive relevance of CTCs for the metastatic situation has already been described [2]. Just like existing distant metastases, circulating tumor cells can show phenotypic features that differ from the primary tumor [3–5]. However, actual therapy decisions are based on the phenotype of the primary tumor or the solid metastases; a characterization of CTCs regarding potentially important predictive attributes such as hormone receptor (HR) or HER2 status is not yet established in the clinical routine.

In DETECT III, patients with a HER2-negative MBC and at least 1 HER2-positive CTC are additionally treated with lapatinib in order to evaluate the benefit of this supplementary HER2-targeted therapy. Patients with HER2-negative MBC and exclusively HER2-negative CTCs are recruited to the DETECT IV trial. The aim of this study is to gain more data on the efficacy and safety of everolimus (DETECT IVa) and eribulin (DETECT IVb) respectively. In the multi-center, randomized phase III study DETECT V/CHEVENDO, an endocrine therapy will be compared with a chemotherapy, each in combination with a dual HER2-directed therapy with trastuzumab and pertuzumab, in women with hormone receptor-positive and HER2-positive MBC (CHEmotherapy VERSus ENDOcrine therapy). The primary endpoint of this study is quality of life, which is measured based on the number of adverse events that particularly impair the patients’ well-being during the treatment.

In addition, the extraction of blood samples at multiple predefined points in time will result in a large amount of available biomaterial. Together with the long-term collection of data on survival and tumor progression, the biomaterial enables the realization of multiple translational research projects. The aim of these projects is to obtain additional information about the biological attributes of CTCs in order to improve existing therapy concepts and to define the value of CTCs with regard to diagnosis, prognosis, and therapy responsiveness. The characterization of CTCs will be performed based on investigations of protein expression (e.g. for the androgen receptor), and via mutation analysis of factors involved in the PI3K/Akt/mTOR signal transduction pathway, which is associated with the development of resistance against endocrine and targeted therapies [6].

These research projects aim to broaden the understanding of CTCs as a liquid biopsy component as potential predictive marker to establish long-term individualized therapies with the aim of an extended progression-free survival and/or an improved quality of life.

References

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