

EUDRACT-NO.: 2010-024238-46	Protocol No.: D-III
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Coordinating Investigator („Leiterin der klinischen Prüfung“ acc. to German Drug Law): Prof. Dr. Tanja Fehm, University Hospital Düsseldorf, Moorenstraße 5, D-40225 Düsseldorf	
Title: 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	
Investigational medicinal product (IMP): Lapatinib tablets 250 mg	
Treatment Plan <u>General:</u> During the randomized treatment period all patients receive a standard chemo- or endocrine therapy combined with or not combined with the IMP lapatinib. The treatment with lapatinib can be extended if medically indicated. The drug will be supplied by Novartis Pharma GmbH on study terms for the duration of the individual study participation (including 2-year-period of follow-up assessments). Generally during the follow-up period treatment is at the discretion of the responsible investigator. <u>Treatment with lapatinib (during Randomized Treatment Period):</u> Lapatinib is only administered to patients randomized to a treatment with lapatinib in addition to a standard chemo- or endocrine therapy. Patients are instructed to take lapatinib once daily at approximately the same time each day and at least 1 hour before or at least 1 hour after a meal. The daily dose of lapatinib depends on the chosen standard chemo- or endocrine therapy. Only dose combinations are allowed that are either approved or that have been investigated in prior clinical trials. The recommended treatment regimens are displayed in the table below.	
Lapatinib + Monochemotherapy	Recommended treatment regimen
lapatinib + docetaxel	Daily lapatinib 1250 mg + docetaxel 75 mg/m ² d1 q3w. Duration of the treatment with docetaxel is at the discretion of the investigator. After discontinuation of docetaxel lapatinib mono 1500 mg daily. Primary prophylaxis with G-CSF should be administered with lipegfilgrastim (Lonquex®) 6 mg 24 h after treatment with docetaxel unless there are no contraindications.
lapatinib + paclitaxel	Daily lapatinib 1500 mg + paclitaxel 80 mg/m ² /weekly, or daily lapatinib 1500 mg + paclitaxel 175 mg/m ² d1, q3w. Duration of the treatment with paclitaxel is at the discretion of the investigator. After discontinuation of paclitaxel lapatinib mono 1500 mg daily.
lapatinib + capecitabine	Daily lapatinib 1250 mg + capecitabine 2000 mg/m ² d1-14, q3w. Duration of the treatment with capecitabine is at the discretion of the investigator. After discontinuation of capecitabine lapatinib mono 1500 mg daily.
lapatinib + vinorelbine	Daily lapatinib 1000 mg + vinorelbine p.o.* 50 mg/m ² d1, 8 q3w. Duration of the treatment with vinorelbine is at the discretion of the investigator. After discontinuation of vinorelbine lapatinib mono 1500 mg daily.
lapatinib + NPLD (non pegylated liposomal doxorubicin)	Daily lapatinib 1250 mg + NPLD 60 mg/m ² d1 q3w. Duration of the treatment with NPLD is at the discretion of the investigator. After discontinuation of NPLD lapatinib mono 1500 mg daily.
Lapatinib + Monoendocrine therapy	Recommended treatment regimen
lapatinib + aromatase inhibitors (AI)	Daily lapatinib 1500 mg + AI as recommended for monotherapy

Table 1: Recommended treatment regimen for combination with lapatinib

*In case of contraindications to the treatment with orally administered vinorelbine, intravenous vinorelbine 20 mg/m² d1, 8 q3w in combination with daily lapatinib 1.250 mg p.o. may be applied instead.

After treatment has been started, the daily dose of lapatinib may be adjusted dependent on the dose regimen of the standard chemo- or endocrine therapy and on the occurrence of adverse events.

In any case, the maximum daily dose is 1500 mg, the minimum daily dose is 750 mg.

Duration of lapatinib therapy is 12 months, unless disease progression or other criteria for premature discontinuation occur. After randomized treatment period the treatment with lapatinib can be extended if medically indicated. The drug will be supplied by Novartis Pharma GmbH on study terms for the duration of the individual study participation (including 2-year-period of follow-up assessments).

Standard Chemo- or Endocrine Therapy (during Randomized Treatment Period):

During the randomized treatment period all patients receive a standard chemo- or endocrine therapy whether they are allocated to lapatinib treatment or not.

Standard chemo- or endocrine therapy is performed in accordance with the Working Group for Gynecological Oncology (AGO) guidelines. The decision for the appropriate standard chemo- or endocrine therapy in individual patients is independent from this clinical trial. However, patients are only eligible for randomization in this clinical trial if standard agents and dose regimens are administered whose combination with lapatinib is either approved (see SPC of Tyverb® 250 mg tablets) or has been investigated in prior clinical trials. The dose of standard chemo- or endocrine treatment should be equal to the combination arm (see table 2).

Duration of standard chemo- or endocrine therapy depends on the agents and dose regimes chosen as well as on the occurrence of tumor progression or other criteria for discontinuation.

Monochemotherapy	Recommended Dosing
Docetaxel	75 mg/m ² i.v. d1 q3w
Paclitaxel	80 mg/m ² i.v. weekly <u>oder</u> 175 mg/m ² d1 q3w
Capecitabine	2 x 1000 mg/m ² p.o. d1-14 q3w
Vinorelbine	50 mg/m ² p.o.* d1+d8 q3w (dose escalation according to patient's tolerance)
NPLD	60 mg/m ² i.v. d1 q3w
Monoendocrine therapy	Recommended Dosing
Exemestan	25 mg/d p.o.
Letrozol	2,5 mg/d p.o.
Anastrozol	1 mg/d p.o.

Table 2: Treatment options for monochemo- or endocrine treatment within DETECT III

*In case of contraindications to the treatment with orally administered vinorelbine, intravenous vinorelbine 20 mg/m² d1, 8 q3w may be applied instead (dose escalation according to patient's tolerance).

Concomitant Treatment of Bone Metastases with Denosumab:

All patients with bone metastases should be treated with denosumab (Xgeva® 120 mg s.c. q4w). Unless there are no contraindications (i.e. severe, untreated hypocalcaemia or hypersensitivity to denosumab/any of the excipients) patients being on bisphosphonates prior to study start will be switched to denosumab. After randomized treatment period the treatment with denosumab can be continued

Treatment in Follow-Up Period:

Therapy after randomized treatment period (i.e. treatment in the follow-up period) is at the discretion of the investigator.

Indication

Metastasizing breast cancer with indication for standard anticancer therapy and with HER2-positive circulating tumor cells (CTC) although the primary tumor tissue and biopsies from all metastatic sites and locoregional recurrences that were investigated for HER2 status showed HER2-negativity.

Clinical trial population

Female patients aged ≥18 years suffering from metastatic breast cancer with indication for standard anticancer therapy.

Objectives of Clinical Trial

The primary objective of the trial is to prove the clinical efficacy of lapatinib (as assessed by the CTC clearance rate) in patients with metastasizing 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:

CTC clearance rate: Proportion of patients with at least one CTC detected in 7.5 ml of peripheral blood drawn before

treatment that show no evidence of CTCs in the blood after treatment (CTC prevalence as assessed using the Cell-Search® System; Veridex LLC, Raritan, USA)

Secondary endpoints:

- *Progression free survival (PFS):* Time interval from randomization until progressive disease (PD) or death from any cause, whichever comes first
 - *Overall response rate:* Rate of complete (CR) and partial responses (PR) in patients with whom target lesions were defined
 - *Clinical benefit rate:* Rate of patients who were assessed PR or CR or who had stable disease (SD) for at least 6 months.
 - *Overall survival:* Time from randomization until death of any cause.
 - *Dynamic of CTC:* Descriptive statistics of regular CTC counts.
 - *Quality of life (QoL):* As assessed by evaluation of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires.
 - *Safety and tolerability of lapatinib:* As assessed by evaluation of adverse event (AE) reports.
 - *Level of compliance to study protocol.*
 - *Intensity of pain:* measured by use of numeric rating scale (NRS)
- (CR, PR, SD and PD are defined according to the RECIST Version 1.1 criteria [Eisenhauer 2009])

Clinical Trial Design

A prospective, multicenter, randomized, open-label, two arm phase III study.

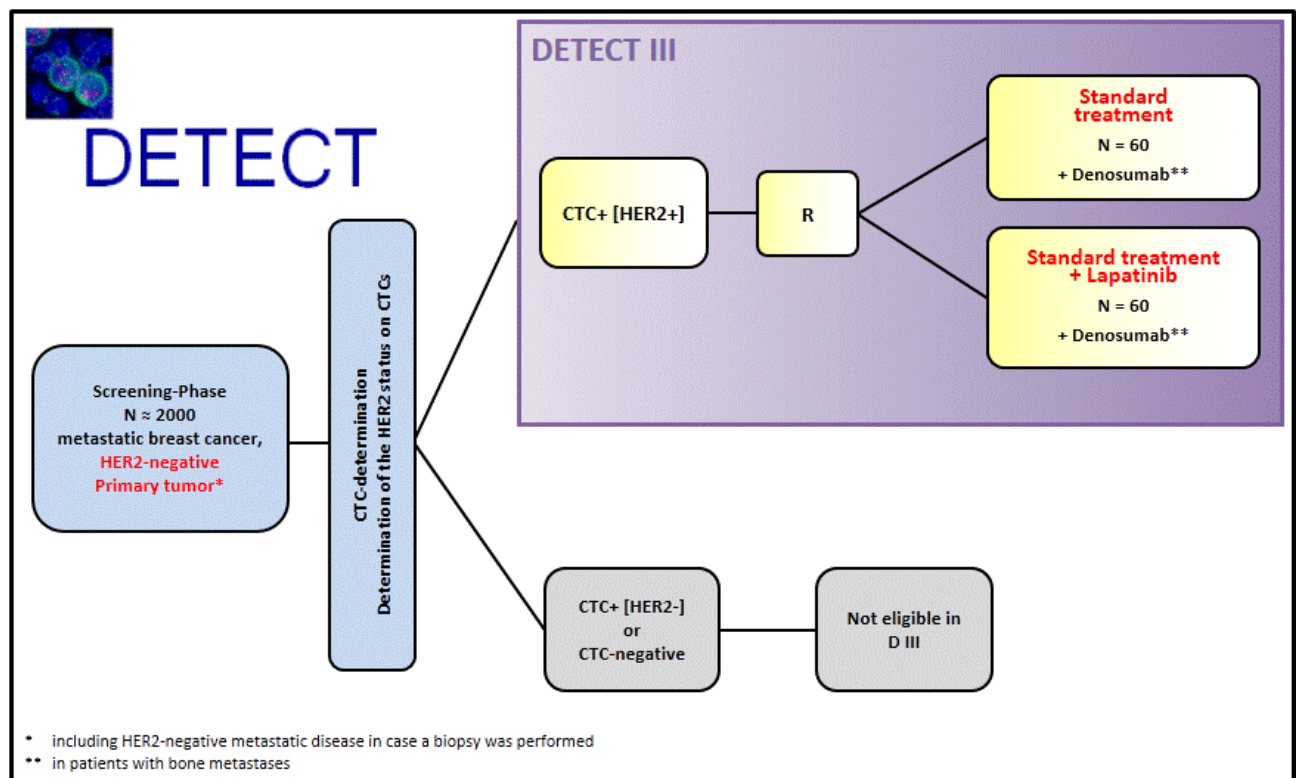


Figure: Clinical Trial Design

Planned duration of the entire study

The study starts when the necessary approval has been given by the competent authority (BfArM). Furthermore the competent ethics committee must have given a favorable opinion on study conduct before the first patient is included. The trial is terminated after death of the last patient.

Accounting for a 72 months recruitment period the maximum study duration is 108 months and 3 weeks (from January 2012 until February 2021).

Planned duration of individual study participation

The individual study participation begins with the screening visit and ends with the patient's death.

- Maximum duration of pre-treatment evaluation period (from screening to randomization): 3 weeks
- Maximum duration of randomized treatment period (from randomization until disease progression or occurrence of other criteria for treatment discontinuation): 12 months

- Estimated maximum follow-up period (from end of randomized treatment until the patient's death): 24 months

The estimated maximum duration of individual study participation is 36 months and 3 weeks.

Number of Clinical Trial Centers Planned to be Involved

A maximum of 100 clinical trial centers is planned to participate in the study.

Inclusion Criteria

1. Written informed consent in study participation.
2. Metastatic breast cancer which cannot be treated by surgery or radiotherapy only. The primary tumor and/or biopsies from metastatic sites or locoregional recurrences must have been confirmed as cancer by histopathology. Estrogen Receptor (EG) and Progesterone Receptor (PgR) status must have been documented.
3. Primary tumor tissue and/or biopsies from metastatic sites or locoregional recurrences were investigated for HER2 status and all of the investigations showed HER2-negativity (i.e.: immunohistochemistry (IHC) score 0-1+ or 2+ and fluorescent in situ hybridization (FISH) negative or just FISH negative, whichever was performed).
In patients for which standard HER2-testing was not available at time of primary diagnosis and for which a biopsy of metastatic sites or locoregional recurrences was not performed are regarded as having a HER2-negative tumor.
4. Evidence of HER2-positive CTCs. Evidence is assumed if the following holds:
 - At least one CTC could be extracted from 7.5 ml patient blood by means of the CellSearch® Circulating Tumor Cell Kit (Veridex LLC, Raritan, USA) and
 - At least one of all extracted CTCs was found to be HER2-positive.
HER2 status must be assessed by means of IHC or FISH.
5. Indication for a standard chemo- or endocrine therapy whose combination with lapatinib is either approved (see SPC of Tyverb® 250 mg tablets) or has been investigated in prior clinical trials (see tables of section 8.2.1.).
6. Tumor evaluation has been performed within 6 weeks before randomization and results are available.
7. Patients must have at least one lesion that can be evaluated according to RECIST guideline version 1.1. Patients with measurable and/or non-measurable disease are eligible. [Eisenhauer 2009].
8. Age \geq 18 years.
9. ECOG Score \leq 2
10. Adequate organ function within 7 days before randomization, evidenced by the following laboratory results below:

• absolute neutrophil count	\geq 1500/ μ L,
• platelet count	\geq 100000/ μ L,
• hemoglobin	\geq 9 g/dL,
• ALT (SGPT)	\leq 3.0 \times ULN,
• AST (SGOT)	\leq 3.0 \times ULN,
• Bilirubin	\leq 2 \times ULN and \leq 35% direct
• creatinine	\leq 2.0 mg/dl or 177 μ mol/L

Please note: These laboratory criteria only refer to lapatinib therapy; with respect to the standard anticancer therapy the relevant summaries of product characteristics (SPCs) have to be observed additionally.
11. Left ventricular cardiac ejection fraction (LVEF) within normal institutional limits as measured by echocardiogram
12. In case of patients of child bearing potential:
 - Negative pregnancy test (minimum sensitivity 25IU/L or equivalent units of HCG) within 7 days prior to randomization
 - Contraception by means of a reliable method (i.e. non-hormonal contraception, IUD, a double barrier method, vasectomy of the sexual partner, complete sexual abstinence). Patient must consent in maintaining such contraception until 28 days after completion of study treatment.

Exclusion Criteria

1. History of hypersensitivity reactions attributed to compounds of similar chemical or biological composition to lapatinib.
2. History of $>$ 3 chemotherapy lines for metastatic disease (a chemotherapy line being defined as any new chemotherapy and any modification of an existing chemotherapy regimen regardless of the reason for change).
3. Treatment with investigational agents of any type or anticancer therapy during the trial or within 2 weeks prior to randomization and 6 weeks in case of nitrosoureas or mitomycin C.
4. Adverse events due to prior anticancer therapy which are $>$ Grade 1 (NCI CTCAE) and therapeutically relevant at time of randomization.
5. Anti-retroviral therapy due to HIV infection.
6. Current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment).
7. Concurrent disease or condition that might interfere with adequate assessment or evaluation of study data, or any medical disorder that would make the patient's participation unreasonably hazardous.
8. Other malignant diseases within the last 3 years apart from CIN of the uterine cervix and skin basalioma.

9. Disease or condition which might restrain the ability to take or absorb oral medication. This includes malabsorption syndrome, requirement for intravenous (IV) alimentation, prior surgical procedures affecting absorption (for example resection of small bowel or stomach), uncontrolled inflammatory GI disease (e.g., Crohn's disease) and any other diseases significantly affecting gastrointestinal function as well as inability to swallow and retain oral medication for any other reason.
10. Active cardiac disease, defined as:
 - History of uncontrolled angina,
 - history of arrhythmias requiring medications, or clinically significant, with the exception of asymptomatic atrial fibrillation requiring anticoagulation,
 - myocardial infarction less than 6 months from study entry,
 - uncontrolled or symptomatic congestive heart failure,
 - ejection fraction below the institutional normal limit,
 - any other cardiac condition, which in the opinion of the treating physician would make this protocol unreasonably hazardous for the patient.
11. Dementia, altered mental status, or any psychiatric or social condition which would prohibit the understanding or rendering of informed consent or which might interfere with the patient's adherence to the protocol.
12. Life expectancy < 3 months.
13. Male patients.
14. Pregnancy or nursing.
15. Primary tumor or biopsies from metastatic sites or locoregional recurrences showing HER2-positivity.
16. Any prior treatment with anti-HER2 directed therapy.

Randomization

All patients, who fulfill the inclusion criteria and exclusion criteria, will be randomized 1:1 to the two treatment arms with SAS: This will be done covariate-adapted using the following stratification factors:

- CTC (< 5 vs. ≥ 5)
- Line of therapy (first vs. at least second).

Clinical Trial Visits

Screening Visit:

- Informed consent in blood sampling for CTC count and assessment of HER2 status on CTC is obtained (patient information and consent form - part 1)*
- Allocation of a patient identification number via eCRF (see also section **Fehler! Verweisquelle konnte nicht gefunden werden.**)*

Data being obtained:

- Year of birth*
- General condition (ECOG, menopause status)**
- Information on primary tumor: date of primary tumor diagnosis*, stage of primary breast cancer*, localization of primary breast cancer**, surgical therapy**
- Information on metastases: date of metastases diagnosis*, localization*, bone/visceral/other*, multiple/single*, surgical therapy**
- HER2 status on primary tumor tissue and/or biopsies from metastatic sites or locoregional recurrences*
- Hormone receptor status found in solid tumor tissue (estrogen and progesterone status each graded positive or negative)*
- Information on adjuvant/neoadjuvant therapy**
- Information on palliative therapy: number of prior chemotherapy lines for metastatic disease*, type(s) of palliative therapy lines**, therapy with bisphosphonates**
- Blood sampling for CTC count and assessment of HER2 status on CTC with **Screening Kit***
 - If CTC count or HER2 status on CTC is negative study participation is terminated (participation in the DETECT IV trial could be possible)
 - If HER2 status on CTC is positive the patient is invited to the Randomization Visit.
- If applicable: additional blood sampling in patients who consent to participate in translational research (part of patient information and consent form – part 1). If a patient objects to blood sampling for this purpose, she may nevertheless participate in the study.

*Data must be obtained within the Screening Visit. In patients for which standard HER2-testing was not available at time of primary diagnosis and for which a biopsy of metastatic sites or locoregional recurrences was not performed are regarded as having a HER2-negative tumor.

**Patients may be screened without obtaining this additional information. Documentation of these data will be reimbursed additionally.

Randomization Visit:

- **Note on Time schedule:** Examinations and data collections for the so-called Randomization Visit are not necessarily to be performed on one single day, but can be done on several days over the following period of time: **From obtaining informed consent - part 2 to day 21 after Screening Visit at the latest.** Results obtained before randomization visit may be employed if they meet the allowed time interval. However, the given flexibility during the Randomization Visit requires exact documentation of time and date of every result.
- If HER2 status on CTC is positive, informed consent in study participation is obtained (patient information and consent form – part 2). Before this no study procedure must be carried out except procedures planned on the Screening Visit.
- In addition, informed consent in blood sampling for translational investigations is obtained (patient information and consent form – part 3). If a patient objects to blood sampling for this purpose, she may nevertheless participate in the study.
- Medical/surgical history, concomitant diseases and ongoing toxicities attributed to prior anticancer therapies (denomination, date of onset, end date / specification if ongoing; in case of toxicities additionally: severity according to NCI CTCAE 4.03, treatment the toxicity is attributed to)
- Prior anti-cancer medication, other relevant prior medication (e.g. treatment of toxicities), concomitant medication (denomination, start date, dosage, route, end date/specification if ongoing, indication)
- Documentation of planned standard chemo- or endocrine therapy (the determination of which is independent from this clinical trial) and check whether combination with lapatinib is either approved (see SPC of Tyverb® 250 mg tablets) or has been investigated in prior clinical trials
- Physical examination
- Vital signs (heart rate, blood pressure, body temperature), height and weight
- Blood sampling for hematology and biochemistry
- Blood sampling for translational medical investigations with **Analysis Kit**, only in patient who have given informed consent – part 3
- Serum or urine pregnancy test
- Tumor evaluation
- Cardiac investigations
- Quality of life assessment
- Intensity of pain assessment
- Review of the inclusion or exclusion criteria.
 - If during pre-treatment evaluation period a patient is found not to be eligible due to one of the inclusion or exclusion criteria, she is excluded from the study. Beyond the respective finding and the respective inclusion or exclusion criterion no further data need to be documented in the eCRF.
 - If the patient meets all inclusion criteria and none of the exclusion criteria, she is eligible for randomization and for protocol treatment.
- Dispense of lapatinib only for patients randomized to lapatinib treatment immediately prior to start of randomized protocol treatment.
- Randomized protocol treatment starts for eligible patients within one week of randomization.
- Adverse events

Control Visits:

- Every 3 or 4 weeks (21/28+3 days) depending on standard treatment: Patients with chemotherapy +/- Lapatinib q3 or 4 weeks depending on therapy schedule. Patients with endocrine therapy +/- lapatinib q 3 weeks:
 - Vital signs
 - Physical examination
 - Adverse events
 - Documentation of protocol treatment (standard therapy +/-lapatinib)
 - Concomitant medication
 - Blood sampling for hematology and biochemistry
 - Quality of life assessment: EORTC QLQ-C30 and EORTC QLQ-BR23
 - Intensity of pain assessment
 - Tablet count, additional dispense of lapatinib if necessary
 - Survival
- The determination of CTCs during cytotoxic treatment should be performed together with evaluation of therapy response since the correlation between CTC count and therapy response will be investigated. Every 8 to 12 weeks after initiation of palliative treatment based on the individual treatment schedule or if medically indicated:
 - Tumor evaluation
 - Blood sampling with **Analysis Kit**
 - for CTC count and assessment of HER2 status on CTC and
 - only in patients who have given informed consent - part 3 also for translational medical investigations
- In case of endocrine treatment every 3 months or if medically indicated until the study endpoint has been reached:

- Tumor evaluation
- Blood sampling with **Analysis Kit**
 - for CTC count and assessment of HER2 status on CTC and
 - only in patients who have given informed consent - part 3 also for translational medical investigations

Conclusion Visit of the Randomized Treatment Period:

- As soon as possible after disease progression or premature discontinuation of protocol treatment or 12 months after randomization:
 - Vital signs
 - Physical examination
 - Adverse events
 - Concomitant medication
 - Documentation of end of protocol treatment (standard therapy +/-lapatinib) and planned therapy after end of protocol treatment
 - Blood sampling for hematology and biochemistry
 - Blood sampling with **Analysis Kit**
 - for CTC count and assessment of HER2 status on CTC and
 - only in patients who have given informed consent - part 3 also for translational medical investigations
 - Cardiac investigations
 - Quality of life assessment: EORTC QLQ-C30 and EORTC QLQ-BR23
 - Intensity of pain assessment
 - Tablet count, collection of unused lapatinib
 - Survival
 - Reminding patient of the follow-up procedures planned

Follow up assessments:

- Between 2 and 4 weeks after Conclusion Visit of the Randomized Treatment Period and then every 3 months:
 - Adverse events which are \geq grade 3 NCI CTCAE and/or serious
 - Concomitant medication
 - Survival

Sample size estimation and principles of analysis

Study Populations

Modified Intention to Treat (mITT) = Safety population: All randomized subjects who received at least one dose of the respective study treatment (chemotherapy or endocrine therapy alone; chemotherapy or endocrine therapy + lapatinib).

Per Protocol (PP): All patients of the mITT set who did not violate any inclusion or exclusion criteria and who were treated according to protocol.

Statistical Methods

Statistical analysis of experimental data will be done at the end of the study. The analysis of efficacy will be based on the patients in the mITT set and the PP set. The safety analysis will be conducted on all patients who received at least one dose of the study treatment. The confirmatory analysis of the primary endpoint will be conducted on the mITT set.

Variables of interest will be determined for each study participant. Best overall response will be assigned as described in section 10.2.1. Time to event endpoints will be assigned to the date of documented event occurrence. In the absence of such documentation, these endpoints will be censored on the last known event-free date.

The primary endpoint CTC clearance rate will be evaluated using non-parametric statistical methods appropriate for the analysis of frequencies and rates (i.e. Chi-square tests and modifications thereof). The proportion of patients that show no evidence of CTCs in the blood after the study treatment will be compared between the two treatment arms, and relative risks, odds ratios and their 95% confidence intervals will be reported.

All parameters regarding secondary endpoints will be evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. If p values are calculated (e.g. in subgroup comparisons or across treatment arms), they will be presented explicitly without referring to hypotheses or a significance level.

Efficacy, toxicity and other event rates are calculated, providing confidence intervals. In case of comparison between patient subgroups, these rates will be analyzed by Cochran-Mantel-Haenszel tests. Event related data like progression free survival, time to progression, duration of response and overall survival time will be estimated by the Kaplan Meier product limit method and compared using the logrank test. For the median values of progression-free or overall survival the 95% confidence interval will be calculated. Multivariate analyses may be performed by suitable regression models (proportional hazard regression model, logistic regression).

The quality of life will be analysed according to the manual of the respective questionnaire.

All p values will be two-sided if not stated otherwise. The statistical methods described in this section are suited for the

data and distributions usually expected in this type of trials. The suitability will be checked after data entry. If necessary, the statistical method will be modified accordingly.

Sample Size Assumptions

The following assumptions were made in the estimation of the required sample size :

- 54% of patients that show no evidence of CTCs in the blood after treatment with standard chemo- or endocrine therapy (this assumption is based on data from the study NCT00898014EGF30001: Blood Levels of Tumor Cells in Predicting Response in Patients Receiving First-Line Chemotherapy for Stage IV Breast Cancer)
- 1:1 randomization scheme
- one-sided test with Type I error of 5% and 80% power

Under these assumptions, a minimum of 102 subjects (51 per treatment arm) will be required to show an increase of the proportion of patients with no evidence of CTCs after treatment from 54% in the standard chemo- or endocrine therapy arm to 77% in the standard chemo- or endocrine therapy plus lapatinib arm. Assuming a loss to follow-up of about 15%, 120 subjects (60 per treatment arm) have to be randomized.

The following assumptions were made in the estimation of the required number of patients with HER2-negative metastatic breast cancer that have to be screened for the presence of HER2-positive CTCs:

- about 65% of patients with HER2-negative metastatic breast cancer are expected to be positive for CTCs (estimate based on Botteri et al. 2010, Fehm et al. 2010, Pierga et al. 2012)
- about 20% of the CTC positive patients are expected to have at least one HER2-positive CTC (estimate based on recent experience gained since the start of DETECT III)
- about 55% of these patients are expected either to fulfill not all of the inclusion criteria or to meet some of the exclusion criteria (estimate based on own recent experience), thus prohibiting the inclusion in the DETECT III trial

Under these assumptions, about 2000 patients with HER2-negative metastatic breast cancer have to be screened to be able to recruit 120 patients for the DETECT III study.

Interim Analysis

No statistical interim analysis is planned so far. A safety analysis will be performed by the coordinating investigator and the DSMB after recruitment of 15 patients in both the HER2-targeted arm and the standard treatment arm.