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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

DETECT III

In cooperation with

This study has been designed according to the 'International Conference on Harmonization Good Clinical Practice Guideline 1998'(1)

EudraCT Number 2010-024238-46

ClinicalTrials.gov Identifier: NCT01619111

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Date	Name	Signature

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("Leiterin der klinischen Prüfung" according to § 4 (25) German drug law)

12.03.2018	Prof. Dr. Tanja Fehm	
Date	Name	Signature

Statistician:

12.03.2018	PD Dr. Thomas Friedl	
Date	Name	Signature

Principal Investigator at the Study Site:

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resources to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents.

I will provide copies of the protocol and access to all further available information on the trial to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

The contents may not be used in any other clinical trial and may not be disclosed to any person except study personnel who will be committed to secrecy. Any supplemental information that may be added to this document is also confidential and must be kept in confidence in the same manner as the contents of this protocol.

I am informed that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study subjects. However, I will give prompt notice to the coordinating investigator. The sponsor and the coordinating investigator may terminate the study at any time with or without stating a cause.

I understand that the coordinating investigator cares for the request of study approval by the competent authority and of a favorable opinion from the competent ethics committee. Before these have been obtained no patient will be included in the trial. The CRO will notify the local authority as required by §67 AMG in conjunction with § 12 GCP-V. I will inform the CRO about any change in study personal, so that the notifications can be done timely.

_____
Principal Investigator

_____
Site Address

_____	_____	_____
Telephone No.	Fax No.	E-mail Address

_____	_____
Date	Principal Investigator's Signature

_____	_____
Date	Representative Signature

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AGO	“Arbeitsgruppe gynäkologischer Onkologen” (Working Group for Gynecological Oncology)
AI	Aromatase Inhibitor
ALT (SGPT)	Alaninaminotransferase
AMG	Arzneimittelgesetz (German drug law)
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartataminotransferase, (Glutamic Oxalacetic Transaminase)
AUC	Area under the (Concentration - Time) - Curve
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German competent authority)
BP	Bisphosphonates
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CIN	Cervical Intraepithelial Neoplasia
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CR	Complete Response
CT	Computerized Tomograph
CTC	Circulating Tumor Cells
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	Cytochrome P
DOB	Date of Birth
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
ER	Estrogen Receptor
FDA	Federal Drug Authority
FISH	Fluorescent In Situ Hybridization
GCP	Good Clinical Practice
GCP-V	Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (German regulation on GCP)
G-CSF	Granulocyte Colony-Stimulating Factor
GI	Gastrointestinal
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GSK	GlaxoSmithKline
hCG	human Chorionic Gonadotropin
HER	Human Epidermal Growth factor Receptor
IF	Immunofluorescence

IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ISF	Investigator Site File
IU	International Units
IUD	Intrauterine Device
IV	Intravenous
L	Liter
LD	Lesion Diameter
LDH	Lactic Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
mL	Milliliter
MRI	Magnetic Resonance Imaging
MUGA	Multiple Update Gated Acquisition
NCI	National Cancer Institute
NYHA	New York Heart Association
NPLD	Non Pegylated Liposomal Doxorubicin
NRS	Numeric Rating Scale
OD	Once Daily
pCR	Pathological Complete Response
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PgR	Progesterone Receptor
PLD	Polyethylene-glycosylated Liposomal Doxorubicin
PR	Partial Response
PTT	Partial Thromboplastin Time
QOL	Quality of Life
RANKL	Receptor activator of nuclear factor kappa B ligand
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SD	Stable Disease
SGPT	Serum Glutamic-Pyruvic Transaminase
SPC	Summary of Product Characteristics
SPF	Sun Protection Factor
SRE	Skeletal Related Events
SUSAR	Suspected Unexpected Serious Adverse Reaction
TK	Tyrosine Kinase
TTP	Time To Progression

UCG	Ultrasound Cardiogram
YOB	Year of Birth

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

General:

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.

Treatment with lapatinib (during Randomized Treatment Period):

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/m² 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/m²/weekly, or-daily lapatinib 1500 mg + paclitaxel 175 mg/m² 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/m² 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/m² 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/m² 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/m² i.v. d1 q3w
Paclitaxel	80 mg/m² i.v. weekly oder 175 mg/m² d1 q3w
Capecitabine	2 x 1000 mg/m² p.o. d1-14 q3w
Vinorelbine	50 mg/m² p.o.* d1+d8 q3w (dose escalation according to patient's tolerance)
NPLD	60 mg/m² 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 CellSearch® 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.

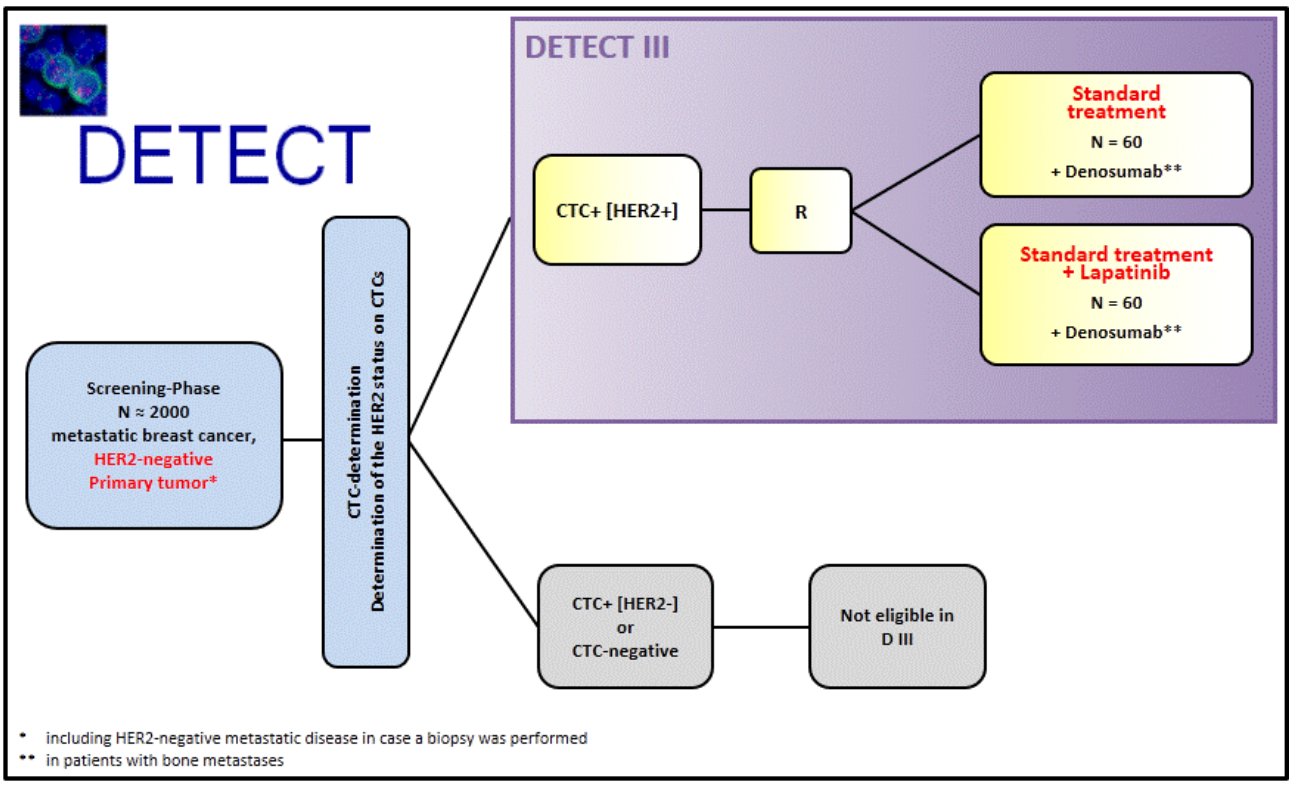


Figure: Clinical Trial Design

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 95 months recruitment period (until 12/2019) the maximum study duration is 131 months and 3 weeks (from january 2012 until january 2023).

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 ≥ 18 years.
9. ECOG Score ≤ 2
10. Adequate organ function within 7 days before randomization, evidenced by the following laboratory results below:
    - absolute neutrophil count ≥ 1500/µL,
    - platelet count ≥ 100000/µL,
    - hemoglobin ≥ 9 g/dL,
    - ALT (SGPT) ≤ 3.0 × ULN,
    - AST (SGOT) ≤ 3.0 × ULN,
    - Bilirubin ≤ 2 × ULN and ≤ 35% direct
    - creatinine ≤ 2.0 mg/dl or 177µmol/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 16.5 Data Protection)*

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

<u>Control Visits:</u>

- 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 ≥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.

1.0 OBJECTIVES

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 or locoregional recurrences that were investigated for HER2 status showed HER2-negativity.

The secondary objective of the trial is to assess the level of compliance to study procedures.

1.1 Primary Endpoint

- Confirmatory analysis is performed by comparison of patients receiving standard anticancer therapy with lapatinib and patients receiving standard anticancer therapy alone, with regard to the following 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 CellSearch® System; Veridex LLC, Raritan, USA)

1.2 Secondary Endpoints

- Exploratory comparison of the efficacy of lapatinib in the given treatment groups with regard to the following 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

  (CR, PR, SD and PD are defined according to the RECIST Version 1.1 criteria *[Eisenhauer 2009].*)

- Assessment of the patients' quality of life (QoL) in both treatment groups with regard to the total score and subscores calculated from data obtained by means of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires.

- Assessment of the safety and tolerability of lapatinib based on adverse event (AE) reports.

- Level of compliance to study protocol.

- Assessment of pain intensity measured by use of a numeric rating scale (NRS)

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Metastatic Breast Cancer

In 2002, an estimated 11 million new cancer cases and 7 million cancer deaths were reported worldwide. Approximately 10% arose in the breast, making it the second most common site of malignant neoplasms after lung and the most common cancer among women. The total number of female breast cancer cases was 1,152,161 with an estimated 411, 932 deaths and a mortality to incidence rate ratio of 0.35. While the incidence rates were nearly three-fold higher in more-developed than less-developed geographic locations (67.8 to 23.8 per 100,000 person years), mortality rates were less than two-fold higher in the former compared to the latter *[Kamanga 2006]*. Despite improvements in early diagnosis and treatment of breast cancer, a significant number of women will relapse and ultimately die of metastatic disease. Recurrent or metastatic breast cancer is an incurable malignancy with a median survival of 20-24 months *[Hortobagyi 1998]* and this has not changed significantly over the last decade with fewer than 20% of patients still alive at 5 years after a diagnosis of recurrence.

The goals of treatment for metastatic breast cancer are to improve survival, prolong progression free survival and promote good quality of life. Although initial treatments did not achieve these goals, in the last decade a number of studies have shown an overall survival benefit. Population based studies have suggested that with the introduction of new contemporary agents, women are living longer after a diagnosis of advanced cancer *[Chia 2007]*. Although response rates and shrinkage of tumors have also been used to determine the activity of a new treatment, a more meaningful endpoint for this patient population in a phase III study would be progression free survival since progression is often symptomatic, increases patient anxiety and requires a change of therapy.

2.2 HER2/neu Positive Breast Cancer

Approximately 15 – 20% of human breast cancers overexpress HER2 (also known as c-erbB2 or neu) oncogene. The HER2/neu gene is located on chromosome 17q21 and encodes for a 185-kd transmembrane protein. Compared to other subtypes of breast cancer, these cancers are associated with a greater risk for disease progression and death *[Meric 2002]* as well as resistance to chemotherapeutic and hormonal agents. Upregulation and autocrine activation of the EGFR and HER2/neu receptors appears to confer an increased resistance to hormonal therapy and cytotoxic chemotherapy *[Slamon 2001]* and a poorer prognosis *[Nicholson 2002]*. HER2/neu overexpression is an independent predictor of shorter disease free survival and overall survival in both node positive and node negative early breast cancer. These cancers are often also poorly differentiated, high-grade tumors, with increased rates of cell proliferation and lymph node involvement *[Burstein 2005]*, more advanced disease at presentation and often occur in younger women.

While until now prognostic implications and possible therapeutic consequences of positive HER2 status were mainly investigated in patients with respective findings in solid tumor tissue, the present study aims to verify possible therapeutic consequences to be drawn from positive HER2 status on CTCs despite no HER2 overexpression in solid tumor tissue.

For assessment of CTC status this study applies the FDA-approved CellSearch® assay, which is currently the most frequently used approach, particularly in on-going clinical trials. It is a semi-automated method based on immunofluorescence. CTCs are isolated by immunomagnetic beads coated with antibodies against EpCAM and identified by cytokeratin-positivity, positive nuclear staining, and CD45 negativity *[Riethdorf 2007]*. It shows high precision and high recovery rates even at low cell levels *[Riethdorf 2007]*. To assure high quality and comparability of HER2 status on CTC, assessments are made by four well experienced central laboratories which have adjusted the method by means of interlaboratory comparisons.

2.3 Lapatinib

2.3.1 Overview of Lapatinib

Lapatinib is an orally active, reversible, small molecule tyrosine kinase inhibitor that potently inhibits both EGFR and HER2/neu tyrosine kinase activity *[Spector 2005]*. Lapatinib differs in enzyme inhibition kinetics from other small molecule tyrosine kinase inhibitors such as gefitinib and erlotinib in that the latter are all rapidly reversible ($t_{1/2}$ < 10 min) whereas lapatinib has a very slow off-rate for both EGFR and HER2/neu (t1/2 > 2 hours) *[Wood 2004]*. *In vitro* studies indicate specificity of lapatinib activity towards the EGFR and HER2/neu targets with resulting tumor growth inhibition.

2.3.2 Safety

Most AEs reported in the lapatinib monotherapy studies in humans were mild to moderate in intensity with the most frequently reported AEs being diarrhea, rash, nausea, fatigue, and anorexia. In studies of lapatinib in combination with chemotherapeutic agents and hormonal agents, the AEs were similar to those seen with each individual agent although the frequency and intensity were greater for certain lapatinib and chemotherapy combinations.

Lapatinib is metabolized in the liver. Hepatotoxicity has been seen with both single agent lapatinib and in combination with chemotherapeutic agents. The AEs that are usually observed are elevations in liver transaminases, but occasionally severe hepatotoxicity has been reported. Abnormal liver function tests usually return to normal once the lapatinib has been stopped but may return on rechallenge with the agent. Rarely deaths have occurred. The current estimate of severe hepatocellular toxicity is 0.1% based on the current experience with 16,562 patients who have received the agent. Mild elevations in liver function tests occur more frequently. Elevated liver enzymes are seen with other tyrosine kinase inhibitors as well.

Cardiac toxicity and pulmonary toxicity are known risks of epidermal growth factor receptor 1 and epidermal growth factor receptor 2 inhibitors. From 17,687 patients included in studies on lapatinib 251 subjects were reported who met the criteria for serious decline in left ventricular ejection fraction (Grade 3 or 4 according to CTCAE version 3.0 criteria or decrease ≥20% from baseline and below the institutional lower limit of normal) and 42 were reported to have experienced pulmonary events suggestive of pneumonitis. This gives an approximate incidence rate of 0.9% for serious decrease in LVEF and 0.2% for pulmonary events.

2.3.3 Clinical Experience with Lapatinib

FDA approval of lapatinib in the USA and CHMP approval in Europe was based on a phase III study [*Cameron* 2007] in 399 patients with pretreated breast cancer refractory to trastuzumab. Patients were randomized to combination lapatinib and capecitabine compared to capecitabine alone. An increased time to progression (TTP) was seen with the combination therapy compared to capecitabine alone (HR=0.57, p<0.001) *[US Package Insert August 2007]*. In addition to systemic antitumor effects, data suggest that lapatinib may have antitumor activity in the central nervous system. Two hundred and thirty seven patients with HER2/neu positive breast cancer and brain metastases with progressive disease or relapse on trastuzumab were treated with lapatinib 750 mg twice daily. Preliminary data demonstrated that 8 patients (7.7%) met volumetric criteria for partial response with a median absolute volume reduction of CNS disease of 3.6 cm^3 (range 0.4 to 29.7 cm^3) *[Lin 2007a]*.

MAPLE is a phase II trial that evaluated antiproliferative effect of preoperative Lapatinib in patients with HER2-positive and HER2-negative/HER3-high primary breast cancer. One hundred twenty-one patients were randomized (3:1) to 10 to 14 days of preoperative Lapatinib or placebo; of these, 21 % were HER2+, 78 % were HER2- non-amplified, 26 % were EGFR+. Biopsies pre-/posttreatment were analyzed for Ki67, apoptosis, HER2, EGFR, ER, PgR, pAKT, pERK and stathmin by IHC. Ki67 levelssignificantly decreased with Lapatinib (-31%; P> 0.001), but not with placebo (-3%). Whereas Ki67 reduction with Lapatinib was the greatest in HER2-positive breast cancer (-46%; P= 0.003), there was also a significant Ki67 decrease in HER2-negative breast cancer (-27%; P=0.017) with 14 % of HER2-negative breast cancer patients demonstrating ≥50 % Ki67 reduction with Lapatinib (Leary et al. 2014).

2.4 Rationale for Current Study

HER2 status of breast cancer may change [Asgeirsso 2007n, Becker 2005, Edgerton 2004, Gancberg 2002, Hayes 2002, Meng 2004, Pestrin 2009, Regitnig 2004, Solomayer 2006, Tewes 2009, Zidan 2005]. It appears reasonable to presume that these patients might benefit from HER2 inhibitors in a similar way as known from patients with HER2-positive primary tumors. Zidan et al. [Zidan 2005] report that 3 out of 7 patients who had HER2-positive metastases but a HER2-negative tumor responded to treatment with the HER2 inhibitor trastuzumab. Meng et al. [Meng 2004] report 4 patients with HER2-negative primary tumor but positive CTC who were treated with the same agent and additional chemotherapy: One patient who was virtually moribund due to renal and liver failure experienced rapid and complete remission, in two patients there was partial remission and one patient suffered progressive disease.

Identification of patients with HER2-negative primary tumor who develop HER2-positive metastases and thus might qualify for HER2 targeted therapy requires regular monitoring of tumor status. Regular tissue sampling appears not

to be feasible in general but assessment of HER2 status on CTC might be an adequate alternative [*Meng 2004, Fehm 2004, Fehm 2009, Tewes 2009]*.

In a previous, prospective multicenter trial, we compared the HER2 status of CTCs in 254 patients with metastatic breast cancer at the time of first diagnosis or disease progression obtained by the antibody-based CellSearch® System. A total of 254 patients with metastatic breast cancer from nine German university breast cancer centers were enrolled in this prospective, open-label, non-randomized study. A total of 245 of 254 blood samples (two 7.5-ml blood tubes) could be analyzed for presence of CTCs by the CellSearch assay. Nine samples had to be excluded due to technical issues: test failure (n = 6), hemolysis of blood sample (n = 2), and insufficient blood volume (n = 1). At least one CTC was detected in 180 of 245 patients (73%) (Table 3). The average number of tumor cells was 177 cells per 7.5 ml (range, 1-6389; median, 4). Using the established cut-off level of 5 cells, 122 of 245 (50%) metastatic patients were considered CTC positive at the time of first diagnosis or disease progression. Presence of CTCs was only associated with extent of metastatic disease ($p < 0.05$). All CTCs were further characterized for HER2 expression within the CellSearch system by addition of an FITC-labeled anti-HER2 antibody. Cases were categorized as HER2-positive CTC if at least five CTCs were detected and at least one CTC showed strong immunostaining (3+) for HER2. Based on this definition, 72 (59%) of the 122 CTC-positive patients, were classified as HER2-negative and 50 (41%) as HER2-positive by immunofluorescence. Correlation of HER2 status between CTCs and corresponding primary tumor was determined. Of those patients with detectable CTCs, primary tumors were HER2-negative in 78 patients and HER2-positive in 31 patients. HER2 status was unknown or inconclusive due to missing FISH analysis in 15 cases. HER2-positive CTCs in HER2-negative primary tumors were seen in 25 of the 78 patients (33%). Discordant HER2 expression was also found in patients with HER2-positive primary tumors, where 13 of 31 (42%) patients had exclusively HER2-negative CTCs. The correlation between HER2 status of CTC and corresponding primary tumor was fair ($P = 0.02$, $\kappa = 0.23$).

In conclusion, HER2-positive CTCs could be detected in a relevant number of patients with HER2-negative primary tumors in this large prospective multicenter study. The proportion of patients with an initially HER2-negative tumor who develop HER2-positive metastatic disease is about 32%. Therefore, it will be mandatory to correlate the HER2 status of CTCs to the clinical response to HER2-directed therapies *[Fehm 2010 a]*.

The present study has been designed against this background. If it succeeds in proving efficacy of lapatinib as anti-HER2 treatment in patients with positive HER2 status on CTCs, but negative primary tumor tissue, this will establish a new strategy in the treatment of metastasizing breast cancer.

Recently, a pilot study was published that specifically evaluated the effect of Lapatinib on HER2-positive CTC counts [Agelaki 2015]. A total of 120 cycles were administered in 22 patients with MBC who present disease stabilization or response after the completion of prior therapy for metastatic disease; median age was 62,5 years. 15 (68,2%) patients were post-menopausal and 20 (90,1%) had a HER2-negative primary tumor. At the end of the second course, HER2-positive CTC counts decreased in 76,2% of patients; the median number of HER2-positive CTCs/patient also declined significantly (P=0.013) However, the decrease was significant only among patients presenting disease stabilization (p=0.018). These results have shown that Lapatinib is effective in decreasing HER2-positive CTCs in patients with MBC irrespectively of the HER2 status of the primary tumor and provide further support for the underlying rationale of the DETECT III study.

2.5 Risk/Benefit Analysis

Risks patients may be exposed due to study participation
If a patient is randomized to treatment with lapatinib the side effects of lapatinib may cause risk according to the well known spectrum of adverse effects of lapatinib. The frequency of adverse effects is well published. There is a very small risk of life threatening side effects.
If patients are not randomized to lapatinib, they are treated as appropriate with their disease. Except for blood sampling for CTC assessments and quality of life evaluations they are not impaired due to study participation.

Benefits accruing to patients by study participation
If patients are randomized to lapatinib, there is a considerable chance that they are treated more efficaciously and profit from prolonged progression free and prolonged overall survival.
If patients are not randomized to lapatinib, study participation entails neither relevant advantages nor relevant disadvantages.

Scientific benefit

The study will increase the knowledge on the role assessment of HER2 status on CTC may play in optimizing therapy of metastasizing breast cancer and on possible effects of lapatinib on CTC in HER2-positive patients. If the combination of a standard chemotherapy and lapatinib is shown to be efficacious, this will show a way to more success in the treatment of metastasizing breast cancer.

Risk/benefit assessment
Anticancer therapy generally is associated with considerable side effects. The potential benefit of increased efficacy of a HER2-neu targeted treatment in the studied patient population would be of high relevance given the unfavorable prognosis of the patients in this study. Taking into account possible benefits resulting from the study, the risks of the study appear acceptable.

2.6 Quality of Life

Quality of life (QoL) is relevant to metastatic cancer patients. From the patient perspective it measures possible drawbacks and – beyond prolongation of survival – possible benefits from an intervention. It provides additional information compared to measuring adverse events alone *[Huschka 2007, Paul 1991]*.

As measuring tool the EORTC QLQ-C30 + BR23 questionnaire is used. It is designed to capture the multidimensionality of QoL in metastatic breast cancer. The EORTC QLQ-C30 + BR23 is a widely used, cancer specific health-related QoL questionnaire which is well accepted by patients *[Aaronson 1993, Conroy 2004].* It contains five functional subscales (physical, role, cognitive, emotional, social), three multi-item symptom subscales (fatigue, pain and nausea), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact) and a global health measure (physical condition and global QoL). The questionnaire uses 4 and 7-point scales. For evaluation each scale is linearly transformed into a scale ranging from 0 to 100. Convergent and criterion validity has been demonstrated for this questionnaire in metastatic breast cancer *[Bottomlay 2004, McLachlan 1998]* and reliability is adequate *[Aaronson 1993, Hjermstad 1995]*. The EORTC QLQ-C30 + BR23 has been shown to be responsive to change associated with chemotherapy and with disease progression *[Osoba 1998, Lemieux 2007]*. The questionnaire is available in German (see APPENDIX V – QUALITY OF LIFE ASSESSMENTS).

2.7 Correlative Studies: Translational medical investigations

Translational medical investigations will be performed in patients who consent in blood sampling for this purpose (patient information and consent form - part 3). At predefined time points during study participation, peripheral blood will be drawn from the patients and collected in tubes, provided by the sponsor, to investigate as follows:

1. Investigation of circulating HER2 and TIMP-1 and Carboanhydrase 9 (CA IX) as potential serum markers to improve the prognostic impact of CTC detection. Along with every blood examination for CTC, a serum sample will be drawn in order to allow the research on potential serum biomarkers in the context of the clinical setting examined here. HER2 can be detected in serum and may allow the assessment of the response to HER2-targeted therapies *[Fehm 2007].* For the two markers TIMP-1 and Carboanhydrase 9 (CA IX) our preliminary results from the DETECT-I study suggest that both serum markers are able to deliver additional prognostic information to CTC measurements *[Fehm 2010 b].*

2. The phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway which is involved in the regulation of cellular processes required for cancerogenesis is frequently altered in breast cancer. Specific mutations in the catalytic (exon 9) and kinase (exon 20) domains of the PIK3CA gene encoding the catalytic subunit p110α of class 1A PI3 kinases have been demonstrated to activate PI3K/Akt signaling (Isakoff et al. 2005) and might play a role in resistance of patients with HER2-positive tumors to treatment with trastuzumab and lapatinib (Berns et al. 2007, Eichhorn et al. 2008, Kataoka et al. 2010). As Jensen and co-workers very recently reported, PIK3CA gene mutations may be discordant between primary breast cancer and corresponding metastases (Jensen et al. 2010). These results emphasize the importance of analyzing the PIK3CA mutational status in circulating tumor cells (CTC) as well, especially in those CTC surviving HER2-targeting therapy. Therefore, we will analyze HER2-positive CTC derived from primary tumors classified as HER2-negative in the context of the DETECT-III study for activating PIK3CA mutations.

3. A variety of different anti-EGFR antibodies are commercially available, the application of which on tumor tissue, however, yields quite different results mostly without predictive value. Therefore, also for EGFR the analysis of gene amplifications might provide more reliable results with the potential to provide additional information pivotal for therapeutic decisions, especially in the context of the treatment of patients

with lapatinib. Thus far there is only limited information about EGFR expression and gene amplification on CTC. Within DETECT-III, we will analyze CTC-positive samples from metastatic breast cancer of patients enrolled in the DETECT-III study for HER and EGFR gene copy numbers by FISH using the CellTracks Analyzer for evaluation of the results.

4. The characterization of CTC is supposed to give further insight into tumor biology and help to identify potential treatment targets. Blood will therefore be collected and single CTCs will be analyzed immunocytochemically for breast cancer markers. The cells will furthermore be processed by PCR or other methods to determine molecularbiological aspects of the tumor cells.

5. Within the DETECT III trial bone metastatic patients will be treated with the fully human monoclonal antibody against **r**eceptor **a**ctivator of **n**uclear factor **k**appa B **l**igand (RANKL): denosumab. Primary tumor tissue and biopsies from metastatic sites were investigated for their RANK/RANKL-status before; data are very heterogeneous however (Bathia et al. 2005; Trinkaus et al. 2009). Up to now it remains unclear whether CTCs express RANK or RANKL and whether denosumab has an influence on CTCs. Thus we will analyze RANK and RANKL-expression on CTCs by double immunofluorescence and RT-PCR as well as its development during treatment with denosumab.

3.0 BACKGROUND THERAPEUTIC INFORMATION

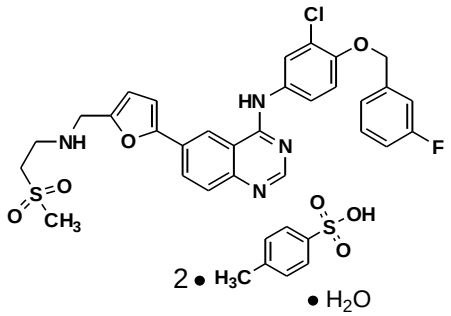
3.1 Investigational Medicinal Product (IMP)

Lapatinib tablets 250 mg (for further information please refer to the investigator's brochure (IB)).

3.1.1 *Name, Chemical and Physical Information*

GW572016F denotes the ditosylate monohydrate salt of the free base, GW572016X. Each tablet contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base per tablet. Refer to the Investigator's Brochure (IB) for information regarding the physical and chemical properties of the drug substance and list of excipients.

Chemical Structure:



Formula: $C_{29}H_{26}ClFN_4O_4S(C_7H_8O_3S)_2H_2O$

Appearance: Yellow, solid.

3.1.2 *Mechanism of Action*

Lapatinib is an orally active, reversible, small molecule tyrosine kinase inhibitor that potently inhibits both EGFR and HER2/neu tyrosine kinase activity.

The human EGF receptor family consists of four transmembrane glycoproteins involved in transmission of signals controlling cell growth and differentiation. EGFR and HER2/neu are closely related members of the Type I family of receptor tyrosine kinases (TK). These growth factor receptors consist of an extracellular ligand binding domain, a single transmembrane domain, an intracellular tyrosine kinase catalytic domain, and a tyrosine rich cytoplasmic tail. Ligand binding induces the formation of receptor hetero- and homodimers with EGFR family members. Dimerization allows the catalytic domain of one receptor monomer to phosphorylate tyrosine residues on the adjacent intracellular domain of the other monomer in the pair. Autophosphorylation of tyrosine residues (p-Tyr) on the cytoplasmic tail creates specific binding sites for SH2 domain containing proteins. The recruitment of SH2 domain containing proteins to the receptor activates signal transduction pathways that initiate cell proliferation *[Ullrich 1990]*. As a result of this signal transduction mechanism, compounds that inhibit the intrinsic tyrosine kinase activity will block the biological activity of the receptor.

Overexpression of EGFR or HER2/neu has been reported in a variety of human tumors *[Davies 1993, Hung 1999]*, and has been associated with poor prognosis and reduced overall survival in patients with cancer *[Slamon 1987, Sainsburry 1985, Salomon 1995]*. Induced over-expression of these receptors in cells *in vitro* produces phenotypes associated with oncogenic transformation such as the ability to grow in soft agar and form tumors in nude mice *[Hudziak 1987, Riedel 1988]*. Thus, a drug that blocks the tyrosine kinase activity of EGFR or HER2/neu should block the transforming activity that results from overexpression of the receptor.

3.1.3 *Experimental Anti-Tumor Activity*

Lapatinib is a potent inhibitor of EGFR and HER2/neu receptor tyrosine phosphorylation in intact cells and is a potent and selective inhibitor of growth in ErbB-driven human transformed cell lines *in vitro* (IC_{90} values $\leq$ 2.66 μM) *[Rushnak 2001]*. It decreases the phosphorylation of EGFR and HER2/neu as well as the downstream signaling

molecules, Akt and Erk1,2, resulting in either tumor cell growth arrest or tumor cell apoptosis *[Rusnak 2001, Konechy 2006]*. Lapatinib is also a potent inhibitor of growth in EGFR and HER2/neu over-expressing subcutaneous tumor xenografts in mice, as well as tumors expressing moderate levels of both receptors; phosphorylated EGFR and HER2/neu reduction was correlated with tumor growth inhibition. *In vivo*, tumor suppression or tumor regression was seen *[Rusnak 2001]*. Thus, the available data support EGFR and HER2/neu receptor tyrosine kinase inhibition as the mechanism of action of lapatinib.

3.1.4 *Indication*

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

3.1.5 *Marketing Authorization Status*

Lapatinib is approved for the combination with capecitabine and for the combination with aromatase inhibitors in the treatment of progressed or metastasizing breast cancer showing over-expression of HER2 receptors (see SPC of Tyverb® 250 mg tablets).

Combinations with other standard anticancer therapies are not approved. However, only combinations will be used in this clinical trial that have been investigated in prior studies (for more information please refer to the table in section 8.2.1).

3.1.6 *Safety*

Adverse Reactions
Adverse reactions observed with administration of lapatinib are given in the following table.
However, it is possible that unknown adverse reactions could occur that vary from person to person. It is not possible to predict in advance if any adverse drug reactions will occur but, if they do, appropriate care will be provided to participants.

Table: Known reactions observed with lapatinib

Reactions attributed to lapatinib	
Incidence	*Description*
≥ 10%	- diarrhea which may entail dehydration - nausea - vomiting - rash (including dermatitis acneiform) - anorexia - fatigue
≥ 1% and < 10%	- decrease in LVEF - nail alterations including paronychia - hyperbilirubinemia - hepatotoxicity
≥ 0,1% and < 1%	- interstitial lung disease, pneumonitis
≥ 0,01% and < 0,1%	- hypersensitivity reaction including anaphylaxis
Reactions known from capecitabine but with increased incidence in case of combination with lapatinib	
Incidence	*Description*
5% greater than with capecitabine alone	- dyspepsia - dry skin
Reactions known from capecitabine and not increased in combination with lapatinib	
Incidence	*Description*
≥ 10%	- stomatitis - constipation

- abdominal pain - palmar-plantar erythrodysesthesia - pain in extremities - backache - sleeplessness - mucositis

Drug Interactions
Lapatinib is a substrate of CYP3A4 and an inhibitor of CYP2C8. Therefore patients treated with lapatinib should not be administered agents inducing CYP3A4 activity or potent inhibitors of CYP3A4. Agents of low therapeutic range which are substrates of CYP3A4 or CYP2C8 should be avoided. In vitro lapatinib was shown to inhibit the transport proteins Pgp, BCRP and OATP1B1. Thus, it may impact the pharmacokinetics of cardiac glycosides, rosuvastatine and other agents.

Combination of lapatinib with paclitaxel may entail severe neutropenia and diarrhea. Close patient monitoring and early treatment of diarrhea are essential.

Solubility of lapatinib depends on pH. Medication increasing stomach pH may reduce the absorption of lapatinib.

For medication not permitted in this study please refer to section 8.4.

Interactions with Food
Grapefruit juice may inhibit CYP3A4 of the intestinal wall und thus increase the bioavailability of lapatinib. Patients who are treated with lapatinib must not drink grapefruit juice.

The fat content of a meal interferes with the bioavailability of lapatinib. Lapatinib must be administered at least one hour before a meal.

Effect on QTc Time
In a dose escalation trial with lapatinib, a slight increase in QTc time was observed. Particular care is required if lapatinib is administered in conditions which might cause QTc prolongation.

3.1.7 *Pharmaceutical Data*

Supply:
Since April 2014 due to the takeover of GlaxoSmithKline's oncology branch the IMP lapatinib is provided by Novartis Pharma GmbH, 90429 Nürnberg in co-operation with the Novartis Pharma Produktions GmbH. Novartis Pharma Produktions GmbH is responsible for shipment of the IMP lapatinib to the clinical trial centers.

Supplier is:

Novartis Pharma Produktions GmbH
Oeflinger Strasse 44
D-79664 Wehr
Germany

Packaging:
Lapatinib tablets 250 mg are oval, biconvex, orange film coated, with one side plain and the opposite side debossed with FG HLS. The 250 mg tablets contain 405 mg of lapatinib Ditosylate Monohydrate (GW572016F), equivalent to 250 mg free base (GW572016X) per tablet.

The tablets are packaged into high density polyethylene (HDPE) bottles with child resistant closures in amounts of 90 tablets within a bottle.

Labeling:
Novartis Pharma GmbH, D-90429 Nürnberg is responsible for labeling of the supplied IMP lapatinib. Each bottle containing 90 tablets with lapatinib 250 mg/tablet will be labeled according to §5 of GCP-V with the following details:

- Warning: "Prüfmedikation - zur Klinischen Prüfung bestimmt"
- Advise "Für Kinder unzugänglich aufbewahren"

- Title of Trial “DETECT III – eine multizentrische, randomisierte, Phase III-Studie zum Vergleich einer Standardtherapie allein versus einer Standardtherapie plus Lapatinib bei Patientinnen mit initial HER2-negativem metastasiertem Brustkrebs und HER2-positiven zirkulierenden Tumorzellen”
- Sponsor Code of Trial Protocol: “D-III”
- EudraCT-Number: 2010-024238-46
- ClinicalTrials.gov ID : NCT01619111
- Subject’s Identification Code “Patienten-Nr. …”
- Subjects Year of Birth "Geburtsjahr: ..."
- Trial Center Number „Zentrumsnummer: …”
- Content specified by quantity “90 Tabletten”
- Name and potency of investigational medicinal product “250 mg Lapatinib pro Tablette”
- Application form “Filmtabletten zur oralen Einnahme”
- Batch number of IMP “Ch.-B. …“
- Expiry date using note “Verwendbar bis …”
- Instructions on required storage conditions “Nicht über 30°C lagern. Vor Lichteinwirkung schützen.”
- Name, address and phone number of the trial sponsor „Universitätsklinikum Ulm, Frauenklinik, Prittwitzstr. 43, 89075 Ulm, Prof. Dr. W. Janni, Tel.: +49 (0)731 500-58501“

A draft label for the IMP lapatinib is presented in APPENDIX XI – DRAFT LABEL FOR IMP LAPATINIB.

Since the daily dose of lapatinib is individually determined and adjusted in each patient, the investigator gives detailed prescription information on the Patient ID Card. A draft Patient ID Card is presented in APPENDIX X – PATIENT ID CARD.

After the end of the transition period Novartis Pharma GmbH, D-90429 Nürnberg is responsible for provision of the IMP lapatinib. From that date on, only german “Handelsware” labeled with a sticker “Zur klinischen Prüfung bestimmt” will be used in the trial.

Stability:
Unopened bottles with lapatinib tablets are stable until the date indicated on the package label when stored under the storage conditions described below.

Storage:
The bottle with lapatinib tablets must be stored in accordance with manufacturer’s instructions below 30°C, dry and protected from light. The principal investigator or the local pharmacist is responsible for correct storage at the clinical trial center.

All trial medication must be kept in a locked area with access restricted to designated trial staff. Persons allowed to handle the study medication are indicated in the site delegation log to be kept in every study center.

Route of Administration:
Oral.

Suspension Preparation:
In exceptional circumstances only, lapatinib may be suspended (dispersed) in water for ease of consumption. The suspension preparation is as follows: Place 120 mL of tap water in a glass container, then add the required lapatinib tablets to the container. Cover the container, let it stand for 5 minutes, and then stir the mixture intermittently for 10 minutes or until it is fully dispersed. Stir the container for 5 seconds then administer. Rinse the container with 60 ml of water and repeat the administration process. This completes the administration process (total of 180 ml of liquid is dispensed).

3.1.8 *Drug Accountability*

The investigator will keep an account of the trial medication and acknowledge the receipt of all shipments of the trial medication. The investigator will also keep accurate records of the quantities of trial medication dispensed, used, and returned by each subject. To assess treatment compliance (please refer also to section 8.2.6) patients are asked to present all tablets not yet used for tablet counts on every visit to the study site. At the end of the treatment period patients must return all unused tablets. At the end of the trial, all unused trial medication and all

medication containers will be completely returned to Novartis Pharma Produktions GmbH or destroyed at the investigator´s site. It will be assured that a final report of the drug accountability is prepared and maintained by the investigator. The site monitor will check this at the close out visit.

The following data are to be recorded:
With every shipment Novartis Pharma Produktions GmbH will provide a drug accounting form and a data log which has to be readout in case of an alert.
On dispensing study medication to the patient: patient identification number, date, batch number, number of tablets, signature of the responsible staff member.
When study medication/packages are returned to the site: Date, number of tablets returned, signature of staff member, who received the medication/packages.
On obliteration of study medication: Amount, date and signature of the responsible staff member.
Drug accountability is documented in the eCRF and the accompanying drug accounting form.

3.2 Standard Chemo- or Endocrine Therapy

3.2.1 *Indication, agents, dose regimens*

Standard chemo- or endocrine therapy is performed in accordance with the Working Group for Gynecological Oncology (AGO) guidelines. However, only agents and daily doses are administered whose combination with lapatinib is either approved (see SPC of Tyverb® 250 mg tablets) or has been investigated in prior clinical trials (see table of section 8.2.1.). Patients can only participate in this clinical trial after decision for a standard chemo- or endocrine therapy fulfilling these inclusion criteria.

3.2.2 *Safety*

With respect to safety, it is possible that unknown adverse reactions that are not yet listed in the respective SPCs of the standard therapies could occur. It is not possible to predict in advance if any adverse drug reactions will occur but, if they do, appropriate care will be provided to participants.

3.2.3 *Rationale for combination of standard chemo- or endocrine therapy with lapatinib*

For the systemic treatment within the DETECT III trial only therapeutic combinations are allowed that are either approved standard treatment according to the regulatory authorities or have already been evaluated in clinical trials. A discussion of toxicity and effectiveness of the single therapeutic treatment options that can be applied within the DETECT III trial is added below.

Combination lapatinib plus docetaxel
Docetaxel is well established as standard treatment option for patients with advanced breast cancer *[Nabholtz 2005]*. The combination of docetaxel and anti-Her2neu targeted treatment with trastuzumab is approved for first line therapy of patients with metastatic HER2/neu-positive breast cancer since June 2004. The DETECT III trial includes the combination of the ERB1 and ERB2-inhibitor lapatinib (1250 mg) in combination with Docetaxel (75 mg/m^2) and thus offers a further treatment option for trastuzumab refractory HER2-positive patients.

LoRusso et al. have evaluated pharmacokinetics, toxicity and optimal tolerated regimen (OTR) within a phase I trial in patients with advanced solid tumors *[LoRusso 2008]*. 50 patients have been enrolled in this study (13% breast cancer) and received a maximum dose of 1500 mg lapatinib once daily and a maximum dose of docetaxel 100 mg/m^2 every 3 weeks in combination with pegfilgrastim. Adverse events were mostly mild to moderate. Drug related adverse events (≥ 25%) were diarrhea (56%), rash (52%), fatigue (27%) and nausea (25%). In conclusion the acceptable optimal tolerated regimen (OTR) of lapatinib plus docetaxel was obtained for a combination of 1250 mg lapatinib once daily plus 75 mg/m^2 docetaxel every 3 weeks together with pegfilgrastim-support.

Table 2. Frequency of All Drug-Related Adverse Events by Maximum Toxicity Grade Occurring in ≥ 10% of All Patients

	% of All Patients (N = 52)					% of Patients at OTR Dose Level (n = 28)				
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Overall	Grade 1	Grade 2	Grade 3	Grade 4	Overall
Diarrhea	42	8	6	0	56	61	7	7	0	75
Rash	42	4	6	0	52	46	0	4	0	50
Fatigue	15	8	4	0	27	14	4	4	0	21
Nausea	19	6	0	0	25	18	4	0	0	21
Mucositis	17	6	0	0	23	25	7	0	0	32
Anorexia	21	2	0	0	23	21	4	0	0	25
Vomiting	15	6	0	0	21	18	7	0	0	25
Neutropenia	0	2	4	10	15	0	0	0	4	4
Leukopenia	2	0	8	4	13	0	0	0	0	0
Pruritus	10	0	0	0	10	11	0	0	0	11
Alopecia	8	2	0	0	10	4	0	0	0	4

Abbreviation: OTR, optimally tolerated regimen.

Source: LoRusso 2008.

There was a complete response reported for 48 patients and partial response for 2 patients. *[Lo Russo 2008]*.

Another multicenter, open-label, phase I/II dose escalation study for the first-line treatment with lapatinib (1250 mg) in combination with docetaxel (75 mg/m^2) has been implemented to assess the safety and efficacy of this treatment regimen in patients with HER2-positive advanced or metastatic breast cancer *[ClinicalTrials.gov identifier: NCT01044485]*. Doses have been calculated on the basis of the EGF 10021 phase I trial, which assessed the combination of lapatinib plus docetaxel and obtained an acceptable optimal tolerated regimen (OTR) of docetaxel (75 mg/m^2) in combination with lapatinib 1250 mg with systemic growth factor support *[ClinicalTrials.gov Identifier: NCT00148902].* The ongoing EGF100161 trial, an open-label, multicenter, phase I/II trial is currently evaluating the OTR of lapatinib combined with docetaxel and trastuzumab in patients previously untreated for ErB2-overexpressing metastatic breast cancer. It obtained hematological toxicities of chemotherapy in combination with lapatinib (1250 mg) and was amended to evaluate lapatinib 1250 mg plus docetaxel 75 mg/m^2 together with systemic growth factor support *[ClinicalTrials.gov Identifier: NCT00251433]*.

In 2010 von Minckwitz et al. published data from the safety run in phase of the GeparQuinto trial, including 60 patients *[Minckwitz 2010]*. The GeparQuinto trial is a phase III trial program exploring the integration of bevacizumab, everolimus (RAD001), and lapatinib into current neoadjuvant chemotherapy regimens for primary breast cancer. Standard neoadjuvant treatment regimen with 4 cycles of epirubicin (90 mg/m^2, q3w) in combination with cyclophosphamide (600 mg/m^2, q3w), followed by 4 cycles of docetaxel (100 mg/m^2, q3w) was combined with either lapatinib (1250 mg) once daily or trastuzumab (loading dose 8 mg/kg, maintenance dose 6 mg/kg, q3w). Results showed that the combined application of lapatinib with EC (epirubicin, plus cyclophosphamide) caused diarrhea, skin changes and hot flushes more frequently than the combined treatment with trastuzumab. In combination with docetaxel the two HER2 targeted agents did not differ in toxicity. Lapatinib at 1250 mg resulted in an increasing rate of treatment discontinuations and was reduced to 1000 mg for protocol treatment *[Minckwitz 2010]*.

Untch et al. recently presented the primary efficacy endpoint analysis of the GeparQuinto trial at the San Antonio Breast Cancer Symposium 2010, evaluating the application of lapatinib in combination with a neoadjuvant anthracycline-taxane-based chemotherapy *[Untch 2010]*. In one treatment arm patients received 4 cycles of epirubicin (90 mg/m^2, q3w) and cyclophosphamide (600 mg/m^2, q3w), followed by 4 cycles of docetaxel (100 mg/m^2, q3w) plus G-CSF combined with lapatinib (1250-1000 mg p.o.) continuously. Significantly more treatment discontinuations occurred in the lapatinib treated patient group due to several reasons (vomiting, nausea, hand-foot-syndrome, diarrhea, fatigue, mucositis and others). Therefore within the GeparQuinto trial a reduction of lapatinib to 1000 mg once a day and special recommendations in case of adverse events were amended. Chemotherapy plus lapatinib resulted in a significantly lower pCR rate of 35% in comparison to chemotherapy with trastuzumab (pCR 50%). In conclusion these data support the need of treatment guidelines in case of adverse events when using simultaneous treatment of lapatinib plus docetaxel *[Untch 2010]*.

The Lapatax trial (EORTC 10054), a phase I study of neoadjuvant lapatinib combined with docetaxel in HER2/neu overexpressing breast cancer has established the maximum tolerated dose (MTD) and has defined the recommended dose for phase II. Doses of lapatinib 1000-1250 mg once daily and of docetaxel 75-100 mg/m^2 every three weeks for 4 cycles have been escalated. The combination of lapatinib and docetaxel during the first 3 dose levels (1000 mg/75 mg/m^2; 1250 mg/75 mg/m^2; 1000 mg/85 mg/m^2) was well tolerated *[Bonnefoi 2008]*.

Cameron et al. are currently investigating the application of neoadjuvant chemotherapy FEC-D with either trastuzumab, lapatinib or their combination for patients with HER2-positive large operable or locally advanced breast cancer to evaluate toxicity and efficacy *[Cameron 2010]*.

These data substantiate the safety and efficacy of the combination of lapatinib (1250 mg) and docetaxel (75 mg/m²) and justify the application.

Combination lapatinib plus paclitaxel

The combined treatment with lapatinib and paclitaxel was evaluated in several large clinical trials. The toxicity profile of a combined administration of paclitaxel and lapatinib is well known and adverse events can be managed according to the protocols recommendations.

DiLeo et al. evaluated the combined therapy of lapatinib (1500 mg) and paclitaxel (175 mg/m², q3w) in a phase III, randomized, multicenter, double-blind, placebo-controlled clinical trial for the first line therapy of patients with metastatic breast cancer *[DiLeo 2008]*. The combination of paclitaxel and lapatinib significantly improved clinical outcomes in HER2-positive patients.

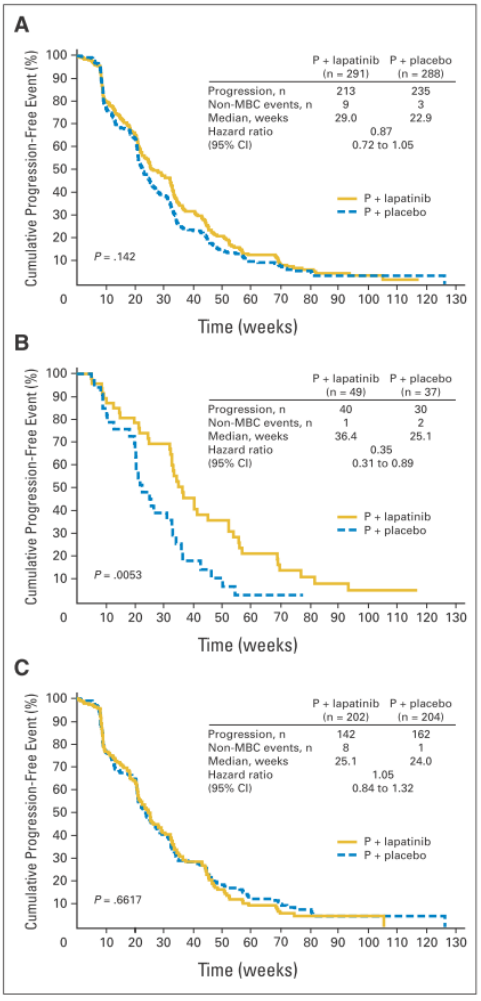


Fig 3. Kaplan-Meier estimates for time to progression. (A) Entire intent-to-treat (ITT) population. (B) Human epidermal growth factor receptor 2 (HER-2) –positive ITT population. (C) HER-2–negative ITT population. The hazard ratio refers to the comparison of paclitaxel (P) plus lapatinib versus P plus placebo. MBC, metastatic breast cancer.

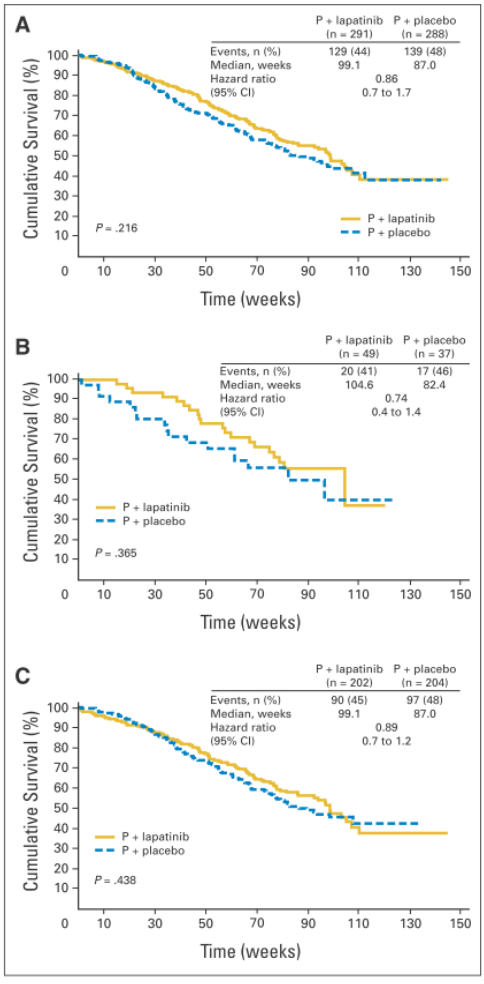


Fig 4. Kaplan-Meier estimates for overall survival. (A) Entire intent-to-treat (ITT) population. (B) Human epidermal growth factor receptor 2 (HER-2) –positive ITT population. (C) HER-2–negative ITT population. The hazard ratio refers to the comparison of paclitaxel (P) plus lapatinib versus P plus placebo.

Source: Di Leo 2008

Most common adverse events were alopecia, rash, diarrhea, nausea, vomiting, myalgia and neutropenia, reflecting the already known adverse events. HER2-negative or HER2-untested patients did not show any benefit from the combined paclitaxel/lapatinib therapy. The addition of lapatinib to paclitaxel resulted in increased grade 3 rash and grade 3 diarrhea. Lapatinib combined with paclitaxel was associated with a 2,7% incidence of fatal adverse events, mainly sepsis associated with diarrhea. Most of these events occurred early in the accrual period. With increased experience in managing drug related toxicity and the introduction of proactive guidelines for managing lapatinib related diarrhea, the incidence and severity of diarrhea episodes could be reduced. These results require increased experience treating the expected adverse events as well as guidelines for managing lapatinib related diarrhea.

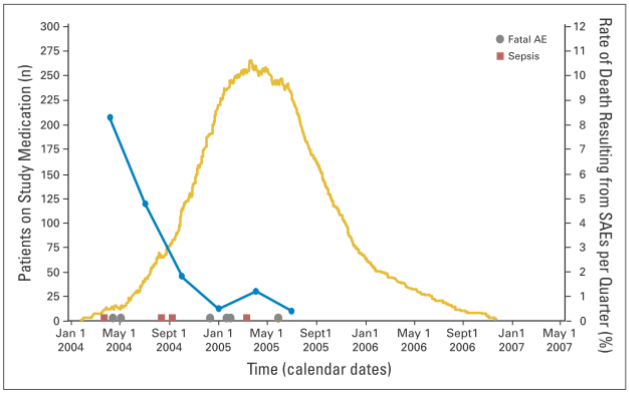


Fig 2. Fatal adverse events (AEs) by time and the number of patients on treatment. SAE, serious adverse event.

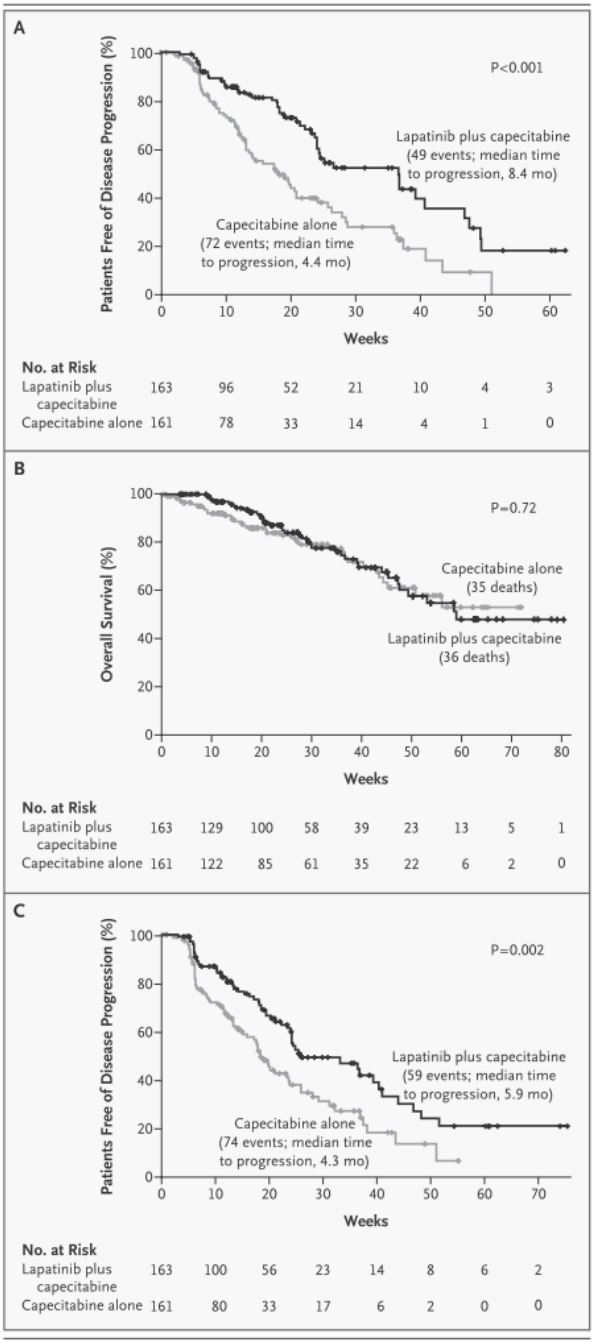
Source: Di Leo 2008

The EGF105764 trial *[ClinicalTrials.gov Identifier: NCT00356811]* and the EGF104535 trial evaluated the combined application of lapatinib 1500 mg/ once daily and paclitaxel 80 mg/m²/weekly and have resulted in no safety concerns due to diarrhea. In conclusion, the results of the EGF105764 trial *[ClinicalTrials.gov Identifier: NCT00356811]* show that the overall response rate according to IRC assessment was 50.9% (95% CI: 37.3, 64.4). Investigator assessment of overall response rate was 77.2% (95% CI: 64.2, 87.3). Responses lasted 37.9 weeks and 42.3 weeks according to IRC- and investigator-review, respectively. Most common adverse events have been diarrhea (56%), neutropenia (44%) and rash (40%). Most adverse events were mild in severity with the exception of neutropenia and ALT increased *[ClinicalTrials.gov Identifier: NCT00356811]*. The EGF104535 trial *[Guan 2008 and Guan 2010]* was evaluating paclitaxel/lapatinib versus paclitaxel/ placebo in the first line treatment of patients with HER2/neu-positive metastatic breast cancer. The median overall survival in the paclitaxel/lapatinib arm was significantly longer than in the paclitaxel/ placebo arm (27.8 months versus 20.5 months, HR [95% CI]: 0.74 [0.58, 0.94], one-sided stratified logrank p-value = 0.0062, two-sided stratified logrank p-value=0.0124). The median progression free survival in the paclitaxel/lapatinib arm was 9.7 months compared to 6.5 months in the paclitaxel/ placebo arm (HR [95% CI]: 0.52 [0.42, 0.64], two-sided p-value=<0.0001). Common adverse events have been neutropenia (77% vs. 47%), diarrhea (77% vs. 29%), rash (59% vs. 24%), leucopenia (53% vs. 33%) and alopecia (46% vs. 51%). The incidence of serious adverse events was 30% in the lapatinib/paclitaxel arm and 14% in the placebo/ paclitaxel arm, most common SAEs were neutropenia (16% vs. 5%), ejection fraction decrease (6% vs. 1%) and diarrhea (5% vs. 0%). There have been no fatal adverse events in the lapatinib/paclitaxel arm compared to 8 fatal adverse events in the paclitaxel/ placebo arm. *[Guan 2008,Guan 2010]*.

Combination lapatinib plus capecitabine

The combined treatment of Lapatinib and capecitabine is an approved treatment option for patients with metastatic breast cancer.

In 2006 Geyer et al. published data from the EGF1001561-trial, a randomized phase III trial examining the treatment combination of capecitabine and lapatinib in patients with metastatic or locally advanced HER2/neu-overexpressing breast cancer, refractory to taxane, anthracycline and trastuzumab therapy *[Geyer 2006]*. The trial evaluated the administration of capecitabine (2000 mg/m²/d (in two divided doses); d 1-14, q3w) in combination with lapatinib 1250 mg versus capecitabine alone (2500 mg/m²/d (in two divided doses), d 1-14, q3w) for patients with HER2-positive advanced breast cancer. Results revealed a superiority of the combined treatment with capecitabine and lapatinib versus capecitabine alone, regarding time to progression (8.4 months versus 4.4 months, HR [95% CI]: 0.49 [0,34 -0,71], p<0,001). *[Geyer 2006]*.



Source: Geyer 2006

Table 2. Efficacy End Points in the Intention-to-Treat Population.*

End Point	Lapatinib plus Capecitabine (N=163)	Capecitabine Alone (N=161)	Hazard Ratio (95% CI)	P Value
Median time to progression — mo	8.4	4.4	0.49 (0.34–0.71)	<0.001†
Median progression-free survival — mo	8.4	4.1	0.47 (0.33–0.67)	<0.001†
Overall response — % (95% CI)	22 (16–29)	14 (9–21)		0.09‡
Complete response — no. (%)	1 (<1)	0 (0)		
Partial response — no. (%)	35 (21)	23 (14)		
Clinical benefit — no. (%)	44 (27)	29 (18)		
Death — no. (%)	36 (22)	35 (22)		

* End points are based on evaluation by the independent review committee under blinded conditions.
† The P value was calculated with the log-rank test.
‡ The P value was calculated with Fisher's exact test.

Source: Geyer 2006

These improvements could be achieved without increase in serious toxic effects or symptomatic cardiac events *[Geyer 2006, SPC]*.

Results of the EGF100151 trial have been updated by Cameron 2008. Compared to capecitabine alone the treatment-combination with lapatinib was able to enlarge the time to progression significantly (HR: 0,57 [95% CI: 0,43, 0,77] p<0,001) and enlarged the progression free survival for patients who initiated protocol therapy within 8 weeks from the last dose of trastuzumab (HR: 0,55 [95% CI: 0,4, 0,74] p<0,001). Results provided a trend towards improved overall survival for the combined treatment arm (HR: 0,78 [95% CI: 0,55, 1,12; p=0,177]). Less progressions regarding the central nervous system occurred within the group of patients treated with lapatinib plus capecitabine (4 versus 13 patients, p= 0,045). No patient group could be identified who failed to benefit from the addition of lapatinib to capecitabine.

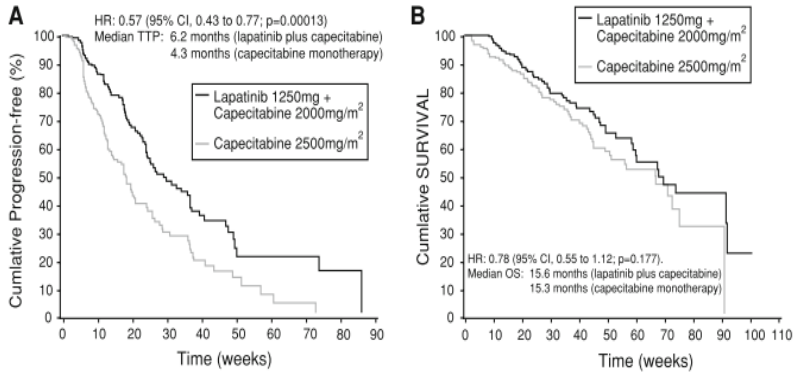
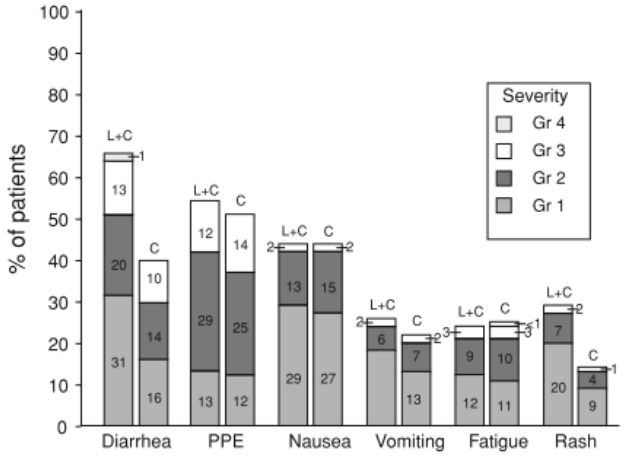


Fig. 2 Kaplan–Meier estimates of time to progression (**a**) (five patients with competing risk were censored for purposes of generating the Kaplan–Meier curve) and overall survival (**b**) in ITT population by Independent Review Committee

Source: Cameron 2008, SPC

The most common adverse events were diarrhea, hand-foot-syndrome, nausea, fatigue, vomiting and rash. Diarrhea and rash occurred more frequently for capecitabine in combination with lapatinib. Dose interruptions and adjustments due to adverse events as well as treatment discontinuations differed only moderately between the two treatment arms.



Source: Cameron 2008, SPC

The final analysis of overall survival for patients treated within the EGF100151 trial was published in 2010. Cameron et al. demonstrated a trend towards a survival advantage with lapatinib plus capecitabine, but no significant benefit (HR: 0,87; 95% CI, 0,71-1,08; p = 0,21). A cox regression analysis considering crossover as a time-dependent covariate suggested a 20% lower risk for death for patients treated with combination therapy (HR: 0,80; 95CI, 0,64-0,99; p = 0,43). Incidence of serious adverse events was low. The data of this clinical trial substantiate the efficacy of lapatinib in patients with HER2-positive metastatic breast cancer. *[Cameron 2010a]*.

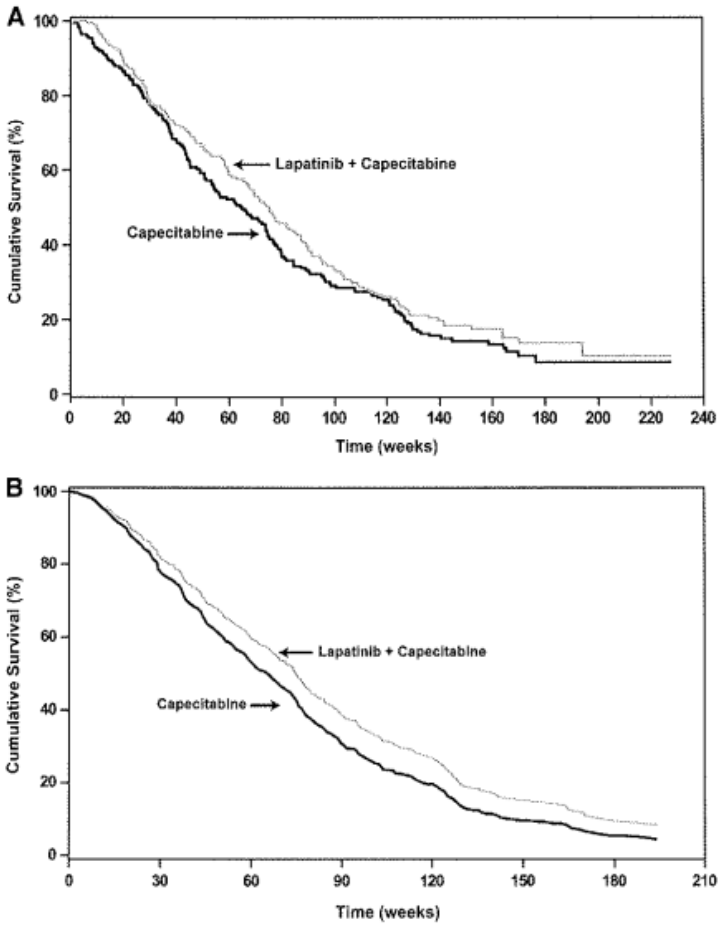


Figure 1. Kaplan–Meier estimates of overall survival (OS). **(A):** Intention-to-treat population. **(B):** OS curve adjusted for Eastern Cooperative Oncology Group performance status score, number of metastatic sites, and liver metastases.

Source: Cameron 2010a

Table 2. Summary of Cox regression model for OS (n = 408)

Covariate	Effect tested	HR (95% CI)[a]	p-value
Treatment group	Lapatinib + capecitabine versus capecitabine	0.81 (0.65–1.00)	.051
Metastatic sites	<3 versus ≥3	0.64 (0.51–0.79)	<.001
ECOG performance status score	0 versus ≥1	0.56 (0.45–0.70)	<.001
Liver metastases	No versus yes	0.52 (0.41–0.65)	<.001

[a]HR <1 indicates a lower risk.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival.

Source: Cameron 2010a

In summary, the combined treatment of lapatinib and capecitabine is approved and established for patients with metastatic breast cancer. The toxicity profile of the combined treatment with lapatinib (1250 mg daily) and capecitabine (2000 mg/m² d1-14, q3w) is well known and well tolerated. Within the DETECT III trial no serious unexpected adverse events are anticipated applying the combined treatment. Dosage and application form of the study medication is adapted to the approved standard treatment recommendations.

Combination lapatinib plus NPLD

The combined treatment regimen of NPLD and HER2 targeting agents have been well investigated within the last 3 years.

Cortes et al. designed a clinical trial to determine the recommended dose of NPLD in combination with trastuzumab, to evaluate cardiac safety and antitumor activity *[Cortes 2009]*. Study results have shown that the combination of NPLD (40-60 mg/kg), paclitaxel (60-80 mg/kg) and trastuzumab (2 mg/kg) is safe and does not cause clinically manifest cardiac toxicity. It has a high response rate in HER2-overexpressing breast cancer. Adding NPLD to the approved trastuzumab/paclitaxel regimen results in high benefit rate in patients with HER2-overexpressing breast cancer and is well tolerated. The overall response rate was 98,1% (CI 95%, 90,1-99,9) with a median time to progression of 22,1 months (CI 95%, 16,4-46,4). *[Cortes: 2009].*

In 2009 Theodoulou et al. published data from a phase I study of nonpegylated liposomal doxorubicin plus trastuzumab in patients with HER2-positive breast cancer *[Theodoulou 2009]*. Preliminary efficacy of NPLD and trastuzumab has been evaluated. NPLD was administered intravenously in a dose of 60 mg/m^2 q3w in combination with a trastuzumab loading dose (4 mg/kg) followed by 2 mg/kg Trastuzumab weekly. Efficacy analysis shows that 50% of the patients had objective tumor responses, median progression free survival was approximately 21 weeks. In conclusions this study revealed that the combined treatment of trastuzumab and NPLD is active and causes less cardiac toxicity than conventional doxorubicin plus trastuzumab *[Theodoulou 2009]*.

In the GEICAM 2003-03 study, a phase II clinical trial of liposomal-encapsulated doxorubicin citrate and docetaxel, associated with trastuzumab as neoadjuvant treatment in stages II and IIA HER2-overexpressing breast cancer patients Anton et al. evaluated the efficacy of this combined treatment regimen *[Anton 2010]*. Patients received 50 mg/m^2 NPLD and 60 mg/m^2 docetaxel every 3 weeks and standard trastuzumab therapy plus pegfilgrastim support. Results have shown the activity of this neoadjuvant treatment regimen with a favorable profile of cardiac toxicity. Clinical and radiological response rates were 86% and 81% *[Anton 2010]*.

Venturini et al. published similar data in 2010 *[Venturini 2010]*. They assessed the cardiotoxicity, general toxicity and activity of NPLD in combination with docetaxel and trastuzumab. Administered doses have been: NPLD (50 mg/m^2), docetaxel 60 mg/m^2 and trastuzumab (2 mg/kg/week) for up to eight cycles. In conclusion data show an acceptable cardiac and general toxicity of this combined regimen and promising activity (median time to progression: 13,0 months) in first-line treatment of patients with HER2-positive metastatic breast cancer *[Venturini 2010]*.

In summary these results are leading to the assumption that a combination of NPLD and anti-HER2 agents might be active and well tolerated.

To gain further options in trastuzumab refractory disease the LAPADO trial *[ClinicalTrials.gov identifier: NCT01172223]* has started recruitment. It evaluates the efficacy and toxicity of a combined treatment with NPLD, lapatinib and docetaxel and gains to determine the optimal doses for NPLD, paclitaxel and lapatinib. The LAPADO trial is an open-label, multicenter, phase I/II trial and includes patients with HER2-positive, invasive breast cancer (T1c N1-2 or T2 N0-2). The administered treatment regimen in the LAPADO trial contains NPLD (Myocet, 60 mg/m^2 i.v. day 1 q3 weeks), paclitaxel (175 mg/m^2 i.v. day 1 q3 weeks) and lapatinib (GW572016, Tyverb, 750-1500 mg/d orally daily until the day of the definitive surgery). Treatment duration is planned for 6 cycles or until disease progression or inadequate efficacy. The phase I part of this trial is already finished, while the phase II part, applying a dosage of 1250 mg lapatinib, 60mg/m^2 NPLD and 175 mg/m^2 paclitaxel is still ongoing. No dose limiting toxicities have been shown, applying a dosage of 1500 mg lapatinib, but neutropenia occurred more frequently in combination with paclitaxel and NPLD *[data not published; ClinicalTrials.gov identifier: NCT01172223]*. Within the Detect III trial 1250 mg lapatinib is administered in combination with 60 mg/m^2 NPLD alone. Based on the phase I data of the LAPADO trial the dosage of 1250 mg lapatinib combined with NPLD alone is expected to be well tolerated.

A pooled analysis of 44 phase I, II and III trials investigated the cardiac safety profile of lapatinib (75-1800 mg) in 3689 patients *[Perez 2008]*. Results showed a decrease of left ventricular ejection fraction in 60 patients (1,6%), 25 patients received lapatinib-monotherapy and 35 received a combined treatment regimen. No cumulative toxicity occurred within the group of patients that received lapatinib for more than 6 months. No case of death was reported due to cardiac toxicity within the lapatinib treated patient group. *[Perez 2008]*.

TABLE 1. **Incidence and Characteristics of Cardiac Events in Lapatinib-Treated Patients, by Prior Anticancer Treatment**[a]

	All patients (N=3689)	Prior anticancer treatment		
		A (n=552)	H (n=826)	Neither A nor H (n=2311)
Any cardiac event, No. (%)	60 (1.6)	12 (2.2)[b]	14 (1.7)	34 (1.5)[b]
Asymptomatic[c]	53 (1.4)	9 (1.6)[b]	13 (1.6)	31 (1.3)[b]
Symptomatic[d]	7 (0.2)	3 (0.5)	1 (0.1)	3 (0.1)
Time to onset (wk)				
Mean ± SD	13±9	16±13	12±8	12±8
95% CI	2-54	3-54	3-32	2-31
LVEF ↓ from baseline to nadir (%)				
Absolute				
Mean ± SD	18.8±5.2	21.3±5.8	17.6±5.5	18.4±4.6
95% CI	11.0-32.0	12.5-32.0	11.0-27.5	11.0-29.0
P value			.15[e]	
Relative				
Mean ± SD	30.0±7.4	32.3±8.1	28.5±6.9	30.0±7.3
95% CI	20.0-52.0	24.0-51.6	20.0-42.3	20.0-52.0
P value			.29[e]	
Patients who recovered (No.)	35	8	8	19
Duration of event (wk)				
Mean ± SD	7.6±10.4	9.3±15.1	7.1±5.5	7.1±10.4
95% CI	0.3-46.0	1.0-46.0	1.7-16.0	0.3-44.0

[a] A = anthracycline-based therapy and no previous trastuzumab therapy; CI = confidence interval; H = trastuzumab-based therapy alone or in combination with chemotherapeutic agents or after anthracycline-based regimens; LVEF = left ventricular ejection fraction.
[b] Two patients experienced 2 cardiac events not heralded by symptoms.
[c] Defined as LVEF decrease ≥20% relative to baseline and below lower limit of normal.
[d] Defined as National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or 4 left ventricular systolic dysfunction.
[e] Calculated among the 3 groups according to Kruskal-Wallis test.[14]

Source: Perez 2008

The common side effects of lapatinib, mainly diarrhea and neutropenia have to be monitored strictly and therapy of any adverse event due to lapatinib should be carried out according to the Detect III protocol's guidelines and the Investigator's Brochure.

Supply: During the randomized treatment period in both treatment arms, Myocet® will be supplied by Cephalon GmbH directly to the participating sites and is to be used exclusively in the clinical study according to the instructions of this protocol.

Combination lapatinib plus vinorelbine

Lapatinib in combination with vinorelbine has been investigated in the GEP01 trial *[Brain 2009]*, a phase I clinical trial in patients with HER2-positive locally advanced or metastatic breast cancer, seeking the recommended dose for combined treatment regimen. Women with progressive disease after 2 or more cycles of trastuzumab have been included in this trial. Therapy was started with a 7 days loading dose of lapatinib before starting vinorelbine (D1 + D8 q3w). Lapatinib was given orally continuously in combination with vinorelbine (D1 + D8 q3w). GCSF-support was permitted. Dose levels ranged from 750 mg/20 mg/m^2 to 1250 mg/30 mg/m^2. Toxicity data was available of 13 patients. Maximal tolerated dose has been reached at 1000 mg/22,5 mg/m^2 for the combined therapy of lapatinib and vinorelbine (D1, D8 q3w). Because of potential pharmacokinetic interference which leads to a higher exposure to vinorelbine, an intermediate dose level is recommended to be explored (1250 mg/22,5 mg/m^2) to allow an accurate definition of recommended dose for combined therapy of lapatinib and vinorelbine in future phase II studies *[Brain 2009]*.

Another phase I study is evaluating the application of two different schedules of lapatinib (GW572016) in combination with vinorelbine in advanced solid tumors *[Chew 2009]*. Study recruitment is closed but results are not finally published. The study objective was based on the assumption of a synergistic effect of lapatinib and vinorelbine on growth-inhibition of tumor cells and intends to find the best dosage (MTD) for combined treatment as well as performing an analysis of toxicity (assessed by NCI CTCTAE v3.0). Patient groups received escalating doses of lapatinib until reaching the MTD. Drug-administration proceeded as follows: In arm A patients received lapatinib orally for 28 days per dose level (250 mg-1500 mg), vinorelbine was given IV Days 1, 8 and 15 per dose level (20 mg/m^2-25 mg/m^2), in arm B patients received lapatinib orally on Days 2-5, 9-12 and 16-25 (1250 mg-1700 mg), and vinorelbine was given IV Days 1, 8 and 15 per dose level (20 mg/m^2-25 mg/m^2) *[Chew 2009]*.

A phase II, single-arm, open-label, multicenter study conducted in the United States evaluated the efficacy of the combination of lapatinib and vinorelbine for first-line or second-line treatment of women with HER2-overexpressing

metastatic breast cancer *[LPT111110 Trial: ClinicalTrials.gov Identifier: NCT00709618]*. 44 enrolled patients received vinorelbine (i.v. D1, D8, D15 q4w) plus lapatinib orally continuously. Treatment was administered until disease progression or withdrawal from the study. The ORR was 41% (95% CI 26-55 %), including 9 % with complete response. Median PFS was 24.1 weeks (95% CI 17-37 weeks) and median duration of response was 32 weeks (95 % CI 18-42 weeks). The most common toxicities were grade 1 and 2 diarrhea, nausea, fatigue and rash, and grade 3 and 4 neutropenia (Chew et al. 2014).
Montemurro et al. published data in 2008 from a retrospective study that investigated vinorelbine for treatment of HER2/neu-positive metastatic breast cancer patients after progression of trastuzumab therapy *[Montemurro 2008]*. Results have shown that vinorelbine based combinations are active and should be further evaluated in studies including trastuzumab-resistant patients for treatment with other HER2 targeting agents. *[Montemurro 2008]*.

Furthermore a current analysis of efficacy of vinorelbine-lapatinib combined treatment is conducted within the VITAL trial *[ClinicalTrials.gov Identifier: NCT01013740]*. Patients with metastatic ERB2-overexpressing breast cancer either receive a combined therapy of lapatinib and capecitabine or of lapatinib and vinorelbine until progression of disease. Within this study patients receive 1250 mg orally once daily continuously and vinorelbine 20 mg/m^2 intravenously D1 and D8, q3w. The dose calculations within the VITAL trial are based on the above mentioned ongoing clinical trials, applying the combined therapy of lapatinib and vinorelbine *[Brain 2009; Chew 2009; LPT111110 Trial: ClinicalTrials.gov Identifier: NCT00709618; VITAL trial: ClinicalTrials.gov Identifier: NCT01013740*]. In this study the total of 112 eligible patients were enrolled; 75 were randomised to lap+vin and 37 were randomised to lap+cap. Median PFS in both arms was 6.2 months. Median OS on Lapatinib plus Vinorelbine was 23.3 months (95% CI 18.5-31.1) and 20.3 months (95 % CI 16.4, 31.8) on Lapatinib plus capecitabine (Janni et al. 2015). Lapatinib plus vinorelbine offers an effective treatment option for patients with HER2-overexpressing MBC, having displayed comparable efficary and toleralibility rates to Lapatinib plus Capecitabine.

The CECOG LaVie phase II trial was set to evaluate the efficacy and safety of venorelbine when combined with Lapatinib as a late-line regimen administered beyond previous disease progression on prior Lapatinib. A total number of nine patients with HER2-positive MBC received Lapatinib at a daily dose of 1250 mg in combination with vinorelbine 20 mg/m^2 i.v. on days 1 and 8 of a three week cycle until disease progression, intolerable toxicity or withdrawal of consent. In this heavily pretreated patient population, the combination of vinorelbine plus Lapatinib showed encouraging activity with a median PFS of 7.7 months (95% CI 0.56-14.91) and a median OS of 23.4 months (95 % CI 16.61-30.13), was characterized by an acceptable safety profile and may thus constitute a potential treatment option in heavily pretreated patients (Thallinger et al. 2016).

Oral administration of vinorelbine might offer several advantages over i.v. treatment. Especially for breast cancer patients whose disease requires prolonged treatment, oral application of vinorelbine is easier and more comfortable.

Marty et al. published the results of a study which was conducted to determine the bioavailability and pharmacokinetics of oral vinorelbine compared to intravenous administration. Oral vinorelbine showed a bioavailability of 40%. Equivalence was demonstrated between 80 mg/m^2 oral and 30 mg/m^2 i.v., and between 60 mg/m^2 oral and 25 mg/m^2 i.v. Based on these data the recommended i.v. dosage of 20 mg/m^2 equates to orally administered 50 mg/m^2.

Additionally the results showed that both forms of administrations exhibit comparable safety profiles. Mainly they induced haematological (leucopenia and neutropenia) as well as gastrointestinal (nausea, vomiting, obstipation, diarrhea) toxicities. The intensity of these side effects was marginally higher after oral application. However, the haematological toxicity did not cause a higher rate of infection.

Lu et al. conducted an open-label, single-arm phase I study to determine the maximum tolerated dose of lapatinib and orally administered vinorelbine. The results of this study recommend lapatinib 1000 mg/day with oral vinorelbine 50 mg/m^2 on day 1, day 8 q3w.

Based on the current study experiences within the DETECT III trial the 3 week cycle dosing schedule of orally administered vinorelbine (50 mg/m^2) on day 1 and day 8 in combination with daily 1000 mg lapatinib is the preferred treatment regimen.

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.
The dose of orally administered vinorelbine needs to be adjusted to the patient's body surface area. Vinorelbin soft capsules are available in the dosage of 20 mg, 30 mg and 80 mg. According to the calculated body surface area (BSA) the absolute dosage of vinorelbine and the appropriate combination of capsules may be seen in the table below.

BSA [m²]	absolute dosage [mg] for 50 mg/m²	type of vinorelbine capsules		
		20 mg	30 mg	80 mg
1,30 – 1,49	70	2	1	0
1,50 – 1,69	80	0	0	1
1,70 – 1,89	90	0	3	0
1,90 – 2,00	100	1	0	1

Body surface area (BSA) should be calculated using actual body weight and not ideal body weight. A maximum BSA of 2.0 m^2 should be used when calculating dosage.

Supply: During the randomized treatment period in both treatment arms, Navelbine® oral will be provided free of charge by Pierre Fabre Pharma GmbH in form of marketed medication directly to the pharmacies of the participating sites and is to be used exclusively in the clinical study according to the instructions of this protocol.

Combination lapatinib plus aromatase inhibitors

The combination of lapatinib and aromatase inhibitors is an approved treatment regimen since 2007. Dose calculations for this regimen are based on a placebo-controlled clinical trial applying lapatinib combined with letrozole versus lapatinib and placebo as first line therapy for postmenopausal hormone receptor-positive and HER2-positive metastatic breast cancer *[Johnston 2009]*. Patients have been randomized to treatment with either daily letrozole (2,5 mg orally) plus lapatinib (1500 mg orally) or letrozole and placebo. The patient group that received the combined treatment of lapatinib and letrozole had a significantly reduced risk of disease progression versus the letrozole-placebo-group (HR: 0,71, 95% CI, 0,53 to 0,96, p=0,019). The trial substantiates the hypothesis that a combined treatment with letrozole and lapatinib enhances the progression free survival and clinical benefit rates in patients with metastatic breast cancer that express HR and HER2 *[Johnston 2009]*.

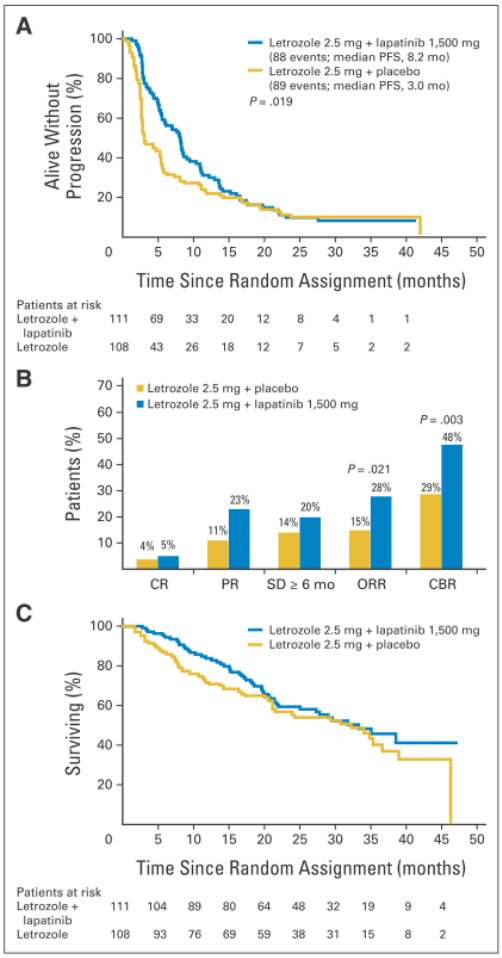


Fig 2. Clinical efficacy in human epidermal growth factor receptor 2–positive population. (A) Kaplan-Meier estimates of progression-free survival (PFS), (B) response rates and clinical benefit rates (CBR), and (C) Kaplan-Meier estimates of overall survival. CR, complete response; PR, partial response; SD, stable disease; ORR, overall response rate.

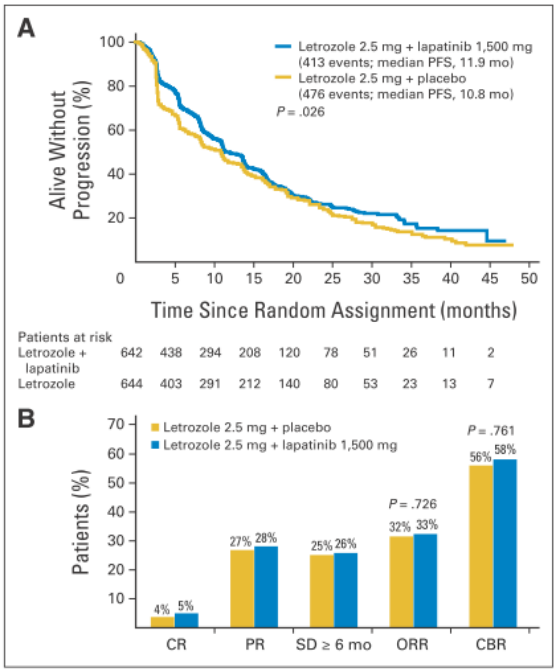


Fig 3. Clinical efficacy in intent-to-treat population. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) response rates and clinical benefit rates (CBR). CR, complete response; PR, partial response; SD, stable disease; ORR, overall response rate.

Source: Johnston 2009

On the basis of this data treatment-combination of lapatinib and aromatase inhibitors is permitted. Optimal dosage of the combined therapy is recommended in the SPC and in that way recommended for application within the DETECT III trial.

3.3 Concomitant treatment of bone metastases with Denosumab

3.3.1 *Indication, agent, dose regimens*

All patients with bone metastases should be treated with denosumab (Xgeva® 120 mg s.c. q4w) unless patients have

- severe, untreated hypocalcaemia (hypocalcaemia must be corrected prior to initiating treatment with denosumab), or
- hypersensitivity to the active substance, denosumab, or to any of the excipients
- non-healed dental or oral surgery as assessed by health care professional
- been submitted to invasive dental procedure without documented healing process in place

Patients being on bisphosphonates prior to study start should be switched to denosumab if they meet all in- and none of the exclusion criteria. Dose regimen: a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen. Administer calcium (at least 500 mg p.o. daily) and vitamin D (at least 400 I.E. p.o. daily) to prevent hypocalcemia.

3.3.2 *Warnings and Precautions*

Hypocalcemia
Administration of denosumab has been associated with hypocalcemia, possibly due to inhibition of osteoclastic bone resorption and a decrease in the release of calcium from bone into the bloodstream. Patients may be most at risk for hypocalcemia within the first 2 weeks after initiation of denosumab.
Hypocalcemia must be corrected prior to initiating therapy with denosumab. In patients predisposed to hypocalcemia, clinical monitoring of calcium levels is recommended. Adequate intake of calcium and vitamin D is important in all patients. Daily oral supplements of ≥ 500 mg calcium and ≥ 400 IU of vitamin D are strongly recommended unless the subject developed on-study hypercalcemia (albumin-adjusted serum calcium > 2.9 mmol/L or > 11.5 mg/dL or ionized calcium > 1.5 mmol/L), as in phase 3 studies the incidences of adverse events of hypocalcemia and grade 3 or 4 reductions in serum calcium were each greater in subjects who did not receive this supplementation.
In the event of clinically significant hypocalcemia, correction may be achieved with intravenous calcium repletion. Oral calcium repletion may be appropriate depending on the clinical circumstances. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcemia. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis.

Osteonecrosis of the Jaw
Because denosumab suppresses bone turnover by inhibiting osteoclast differentiation and activity, its use could potentially lead to an inability to repair bone defects, such as after invasive dental procedures or dental fracture, thereby increasing the risk of ONJ. ONJ has occurred in patients treated with denosumab. A dental examination with appropriate preventive dentistry should be performed prior to treatment with denosumab in patients with risk factors for ONJ. All subjects will be reviewed for oral adverse event regularly (during each physical examination scheduled as per protocol). The administration of denosumab should be withheld for 30 days prior to any elective invasive oral/dental procedure and should not be continued until documented evidence of complete mucosal healing.
Oral adverse events suspicious of ONJ should be examined by a dentist or other qualified oral specialist (eg, oral surgeon) and patients with ONJ should receive specialist care.

There are no adequate and well-controlled trials of denosumab in pregnant women. Patients receiving denosumab should use 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).

3.3.3 *Supply*

After randomized treatment period the treatment with denosumab can be continued. Denosumab has to be prescribed according to its official approval.

3.3.4 *Marketing Authorization Status*

In July 2011 the EMA (European Medicines Agency) approved denosumab for the prevention of skeletal-related events (SREs) in adults with bone metastases from solid tumors. Additionally denosumab treatment of bone metastases in patients with breast cancer is part of the AGO recommendations.

3.3.5 *Safety*

Please refer to the current version of the SPC of denosumab.
In addition, it is possible that unknown adverse reactions that are not yet listed in the current SPC of Denosumab could occur. It is not possible to predict in advance if any adverse drug reactions will occur but, if they do, appropriate care will be provided to participants.

3.3.6 *Pharmaceutical Data*

Packaging and formulation:
The active substance is Denosumab. Denosumab is a solution for injection in a vial. Each vial contains 120 mg of denosumab in1.7 ml of solution (corresponding to 70 mg/ml). The other ingredients are acetic acid, glacial, sodium hydroxide, sorbitol (E420) and water for injections. Denosumab is a clear, colourless to slightly yellow solution. It may contain trace amounts of clear to white particles. Each pack contains one vial.

Storage:
Keep Denosumab out of the sight and reach of children.
Do not use Denosumab after the expiry date which is stated on the label and carton after EXP.
The expiry date refers to the last day of that month. Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original carton in order to protect from light.

Preparation and administration:
The vial may be left outside the refrigerator to reach room temperature (up to 25°C) before injection. This will make the injection more comfortable. Once your vial has been left to reach room temperature (up to 25°C), it must be used within 30 days. Do not throw away Denosumab via wastewater or household waste.
Do not shake excessively.Read the package leaflet before use.
Denosumab is administered as a subcutaneous injection.

3.3.7 *Rationale*

Nearly 80% of patients with metastatic breast cancer develop bone metastases which induce increased activity of osteoclasts. This results in local bone destruction and skeletal complications (e.g. bone pain, pathological fractures or hypercalcaemia). Several randomized trials proved bisphosphonates (BP) to be successful in patients with metastatic breast cancer to prevent skeletal complications (skeletal related events, SRE) *[Body 2003, Pavlakis 2005]* and to significantly improve quality of life *[Diel IJ 2004]*.

However, many patients still develop SREs despite intravenous application of BP-therapy. Patients treated with BP have an increased risk of nephrotoxic side effects *[Chang 2003, Markowitz 2003]* and osteonecrosis of the jaw *[Coleman RE 2008]*. Consequently alternative treatments are needed.

Beside BP denosumab is an option in “bone targeted therapy”. Denosumab is a fully human monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL). RANKL is known to be a key mediator of osteoclast formation and activation *[Lacey 1998]*. Thus denosumab inhibits osteoclast activity which reduces bone resorption.

In 2010 Stopeck et al. evaluated the application of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer conducting a randomized, double-blind phase III study. Patients received either denosumab (120 mg s.c., every 4 weeks) or zoledronic acid (4 mg i.v., every 4 weeks). Results proofed a significant superiority of denosumab in both delaying and preventing skeletal complications compared to zoledronic acid.

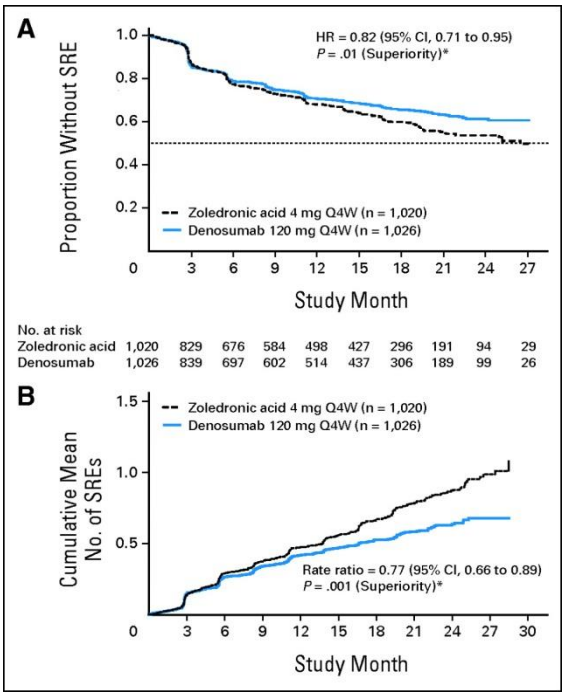


Fig.1: Kaplan-Meier estimates of (A) Time to first skeletal-related event (SRE) and (B) time to first and subsequent SREs (multiple event analysis), which is represented as the cumulative mean number of SREs over time. Drugs were administered every 4 weeks. HR, hazard ratio; Q4W, every 4 weeks. (*) Adjusted for multiplicity. *[Stopeck et al. 2010]*

Based on the current study data denosumab is an important and promising alternative to BP. In July 2011 the EMA (European Medicines Agency) approved denosumab for the prevention of skeletal-related events (SREs) in adults with bone metastases from solid tumors. Additionally denosumab treatment of bone metastases in patients with breast cancer is part of the AGO recommendations.

Concerning the side-effects and toxicity of denosumab data suggest that denosumab bears potentially beneficial characteristics for patients: besides the convenience of a subcutaneous injection compared to the need of an intravenous infusion of BP, renal toxicity occurred less frequently in patients treated with denosumab *[Stopeck 2010]*. Thus, denosumab represents a therapeutic option for patients with renal insufficiency and chronic renal failure. Additionally the incidence of acute-phase reactions (flu-like symptoms) was almost three times higher in patients treated with BP *[Stopeck 2010]*. Osteonecrosis of the jaw (ONJ) is known to be a rare but serious side effect of intravenous treatment with BP. The incidence of ONJ was not statistically different between zoledronic acid and denosumab (p=0,39) *[Stopeck 2010]*. Recommendations for precautions to prevent ONJ (e.g. ensuring a good oral health before initiation of a BP-/denosumab therapy) have been assorted by a committee of the German Society for Senology *[Fehm 2009]*.

Consequently denosumab is expected to be better tolerated than BP and is a novel treatment option as standard therapy for the management of bone metastases in patients with breast cancer within the DETECT III trial.

3.4 Concomitant treatment of neutropenia with lipegfilgrastim

3.4.1 *Indication, agent, dose regimens*

Lipegfilgrastim is used to reduce the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). Primary prophylaxis with lipegfilgrastim is recommended to be administered with doxetacel and lapatinib combination therapy. Otherwise lipegfilgrastim should be used in center´s standard practice according to general recommendations *[Smith 2006]* using G-CSF derivates,
unless patients have

- known hypersensitivity to the active substance, lipegfilgrastim, or to any of the excipients or other G-CSF or derivates
- severe, untreated hypokalaemia (hypokalaemia must be corrected prior to initiating treatment with lipegfilgrastim)
- severe thrombozytopenia, myelogenous leukaemia or splenomegalia
- evidence of pulmonal infiltrates or pneumonia or ARDS (Adult Respiratory Distress Synome)
- sickle cell anaemia

One 6 mg dose of lipegfilgrastim (a single pre-filled syringe of Lonquex) is recommended for each chemtherapy cycle, given approximately 24 hours after cytotoxic chemotherapy. In clinical studies with a limited number of elderly patients, there was no relevant age-related difference with regard to the efficacy or safety profiles of lipegfilgrastim. Therefore, no adjustment of the dose is necessary for elderly patients. No recommendation on a posology can be made for patients with renal or hepatic impairment.

3.4.2 *Warnings and Precautions*

Haematopoietic system

Treatment with lipegfilgrastim does not preclude thrombocytopenia and anaemia caused by myelosuppressive chemotherapy. Lipegfilgrastim may also cause reversible thrombocytopenia. Regular monitoring of the platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic medicinal products that are known to cause severe thrombocytopenia. Leukocytosis may occur. No adverse events directly attributable to leukocytosis have been reported. Elevation in white blood cells (WBC) is consistent with the pharmacodynamic effects of lipegfilgrastim. A WBC count should be performed at regular intervals during therapy owing to the clinical effects of lipegfilgrastim and the potential for leukocytosis. If WBC counts exceed 50 x 109/l after the expected nadir, lipegfilgrastim should be discontinued immediately.

Splenic adverse reactions

Frequent but generally asymptomatic cases of splenomegaly and infrequent cases of splenic rupture, including fatal cases, have been reported following administration of G-CSF or derivatives. Spleen size should therefore be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Pulmonary adverse reactions

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after administration of lipegfilgrastim. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.
The onset of pulmonary symptoms such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function together with an increased neutrophil count may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). In such circumstances Lonquex should be discontinued at the discretion of the physician and appropriate treatment given.

Patients with sickle cell anaemia

Sickle cell crisis has been associated with the use of G-CSF or derivatives in patients with sickle cell anaemia. Physicians should therefore exercise caution when administering Lonquex in patients with sickle cell anaemia, monitor appropriate clinical parameters and laboratory results and be attentive to the possible association of lipegfilgrastim with splenic enlargement and vaso-occlusive crisis.

Hypokalaemia
Hypokalaemia may occur. For patients with increased risk on hypokalaemia due to underling disease or co-medications, it is recommended to monitor the serum potassium level carefully and to substitute potassium if necessary.

Excipients with known effect
This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product. This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially 'sodium-free'.

Interaction with other medicinal products and other forms of interaction
Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, lipegfilgrastim (Lonquex) should be administered approximately 24 hours after administration of cytotoxic chemotherapy. Concomitant use of lipegfilgrastim with any chemotherapeutic medicinal product has not been evaluated in patients. In animal models, concomitant administration of G-CSF and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.
The safety and efficacy of lipegfilgrastim (Lonquex) have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression, e.g. nitrosoureas.
The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

3.4.3 *Supply*
After randomized treatment with lipegfilgrastim can be continued. Lipegfilgrastim may be prescribed according to its official approval. The dosing recommended for Lonquex is 6 mg (a single pre-filled syringe of Lonquex) for each chemotherapy cycle and should be given approximately 24 hours after cytotoxic chemotherapy via the subcutaneous route.

3.4.4 *Marketing Authorization Status*
In July 2013 the EMA (European Medicines Agency) approved lipegfilgrastim for reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

3.4.5 *Safety*
Please refer to the current version of the SPC of lipegfilgrastim.
In addition, it is possible that unknown adverse reactions that are not yet listed in the current SPC of lipegfilgrastim could occur. It is not possible to predict in advance if any adverse drug reactions will occur but, if they do, appropriate care will be provided to participants.

3.4.6 *Pharmaceutical Data*
Packaging and formulation:
Lonquex is a sterile, preservative free solution for injection, containing 6 mg of lipegfilgrastim active pharmaceutical ingredient at a concentration of 10 mg/mL. The concentration is declared based on protein content. Lonquex is presented in a 1 mL type I glass pre-filled syringe to be stored in refrigerator. The solution is formulated with sodium acetate (formed by titrating acetic acid with sodium hydroxide), Sorbitol and Polysorbate 20. The pH is adjusted to 5.0.

Labeling and storage:
Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light. Lonquex may be removed from the refrigerator and stored below 25 °C for a maximum single period of up to 3 days. Once removed from the refrigerator, the medicinal product must be used within this period or disposed of.

Preparation and administration:
The solution should be visually inspected before use. Only clear, colourless solutions without particles should be used. The solution should be allowed to reach a comfortable temperature (15 °C - 25 °C) for injection. Vigorous shaking should be avoided. Excessive shaking may aggregate lipegfilgrastim, rendering it biologically inactive. Lonquex does not contain any preservative. In view of the possible risk of microbial contamination, Lonquex syringes are for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

3.4.7 *Rationale*

Cytotoxic chemotherapy suppresses the hematopoietic system causing profound and sometimes prolonged neutropenia. Chemotherapy-induced neutropenia is the major dose-limiting toxicity of systemic cancer chemotherapy. It may result in hospitalisation for treatment of fever or cause potentially fatal infection. Risk factors for cytotoxic chemotherapy-induced neutropenia are: advanced age, female sex, poor performance status, poor nutritional status and low baseline and first cycle nadir blood cell count along with high chemotherapy dose intensity. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are used to reduce the duration and degree of neutropenia. G-CSF increases the proliferation and differentiation of neutrophils from progenitor cells, induces maturation and enhances the survival and function of mature neutrophils. According to the European Organisation for Research and Treatment of Cancer (EORTC) guideline, primary prophylactic G-CSF treatment is recommended in case the overall risk of febrile neutropenia (FN) for a patient is ≥20%. When using chemotherapy regimens associated with a FN risk of 10-20%, particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN (Aapro et al., EJC, 2006; 42: 2433-53). Evidence from multiple randomised trials supports the benefit of primary prophylaxis in reducing the frequency of hospitalisation for antibiotic therapy, documented infection, and rates of neutropenic fever in adults. The impact on survival is less clear (Kuderer et al., J. Clin Oncol 2007; 25:3158).

Recombinant granulocyte-colony stimulating factor (G-CSF) products have emerged as effective therapies for reducing the duration and incidence of chemotherapy-induced neutropenia and FN by stimulating neutrophil proliferation and differentiation in cancer patients [8,9]. Short-acting r-metHuG-CSFs (e.g., filgrastim) require daily subcutaneous (s.c.) injections during each chemotherapy cycle. The attachment of a polyethylene glycol (PEG) molecule (pegylation) to filgrastim (e.g., pegfilgrastim) decreases plasma clearance and extends the drug's half-life in the body, allowing for less-frequent dosing [10,11]. Placebocontrolled clinical studies have shown significant reductions in the incidence of FN in patients treated with r-metHuG-CSF products [3,9]. Randomized, phase III, comparative studies have demonstrated similar trends in patients treated with once-per-cycle fixed-dose pegfilgrastim compared with once-daily filgrastim [2,12]. Lipegfilgrastim is a onceper-cycle, glyco-pegylated r-metHuG-CSF developed for the prevention of chemotherapyinduced neutropenia. Clinical data have shown lipegfilgrastim (6 mg) to be well tolerated in healthy volunteers, with dose-dependent increases in bioavailability and ANC comparable to that seen in pegfilgrastim (6 mg)-treated patients [13]. In the phase III registration trial (Bondarenko; 2013) demonstrated that a single fixed-dose injection of lipegfilgrastim 6 mg was noninferior to the active control pegfilgrastim in patients with breast cancer receiving myelosuppressive chemotherapy. Overall, this study showed that lipegfilgrastim has a safety profile that is consistent with a G-CSF and acceptable the intended patient population.

4.0 TRIAL DESIGN

This is a prospective, multi-center, randomized, open-label, two arm phase III study.

4.1 Number of Clinical Trial Centers Planned to be Involved

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

4.2 Number of Participating Patients

A total of 120 patients are to be randomized, which is expected to require screening of at least 2000 patients.

4.3 Schedule

Single Patients:
The individual study participation begins with the screening visit and ends with the patient's completion of the follow-up period or with the patient's death.

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

Patient participation is divided in 3 consecutive periods:

Pre-Treatment Evaluation Period:	Content: Examinations and collection of data relevant to decide on patients' eligibility for further study participation. Period: From screening to randomization Maximum duration: 3 weeks Visits: From Screening Visit to end of Randomization Visit
Randomized Treatment Period:	Content: Treatment with a standard chemo- or endocrine therapy combined with or not combined with lapatinib according to randomization. Assessment of efficacy and safety data. Period: From randomization until disease progression or occurrence of other criteria for treatment discontinuation Maximum duration: 12 months* Visits: From Randomization Visit to Conclusion Visit of the Randomized Treatment Period *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).
Follow-Up period:	Content: Assessment of survival, adverse events and concomitant medication. Treatment of the metastatic disease at the investigator's discretion Period: From end of randomized treatment until the patient's death Maximum duration (estimation): 24 months Visits: From Conclusion Visit of the Randomized Treatment Period to the last Follow-Up Visit.

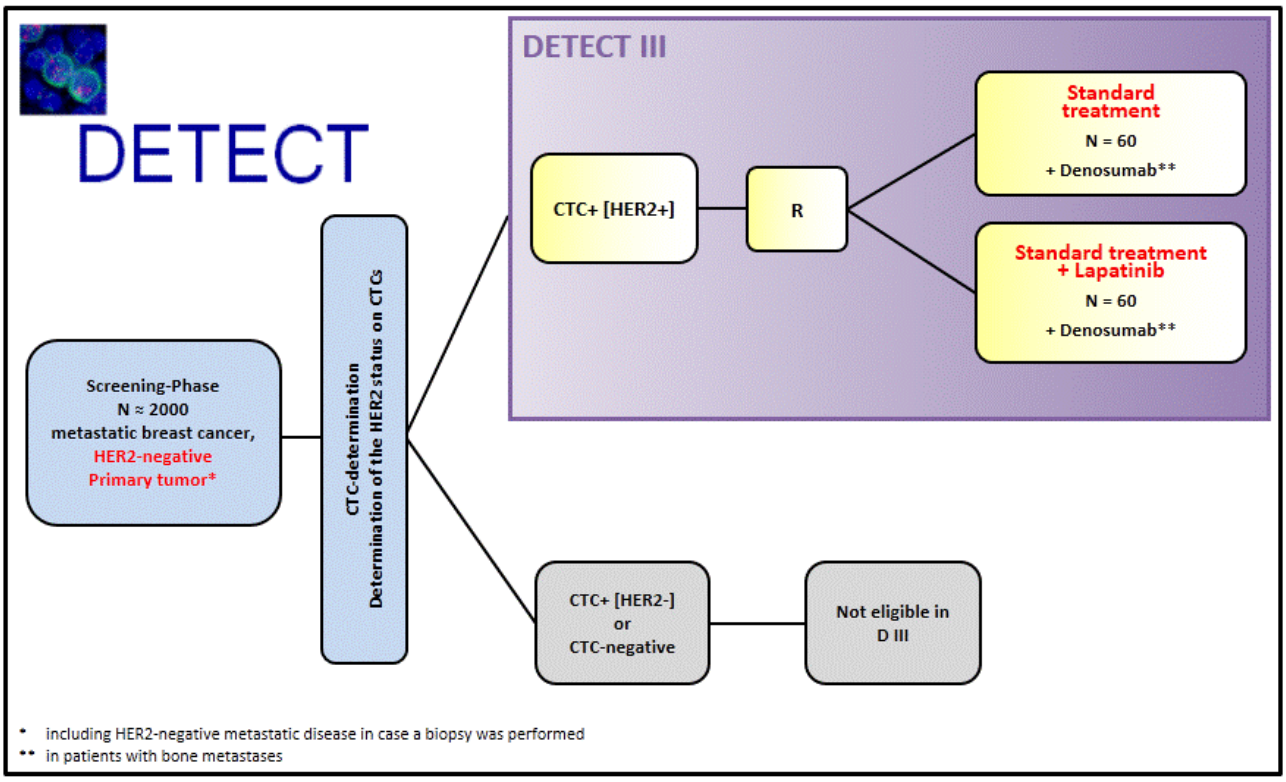


Figure: Clinical Trial Design

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 95 months recruitment period (until 12/2019) the maximum study duration is 131 months and 3 weeks (from january 2012 until january 2023).

4.4 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).

5.0 STUDY POPULATION

Women suffering from metastatic breast cancer and with positive HER2 status in circulating tumor cells but with negative HER2 status in earlier examination of solid tumor tissue.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed PRIOR to requesting randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions are made to these criteria for admission to the study.
Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Written informed consent in study participation.

5.1.2. 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 (ER) and Progesterone Receptor (PgR) status must have been documented.

5.1.3 All primary tumor tissue and/or biopsies from metastatic sites or locoregional recurrences that were investigated for HER2 status 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.

5.1.4 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.

5.1.5 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.).

5.1.6 Tumor evaluation has been performed within 6 weeks before randomization and results are available.

5.1.7 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]*.

5.1.8 Age ≥ 18 years.

5.1.9 ECOG Score ≤ 2.

5.1.10. Adequate organ function within 7 days before randomization, evidenced by the following laboratory results below:
- absolute neutrophil count ≥ 1500/µL,
- platelet count ≥ 100000/µL,
- hemoglobin ≥ 9g/dL,
- ALT (SGPT) ≤ 3.0 × ULN,
- AST (SGOT) ≤ 3.0 × ULN,
- Bilirubin ≤ 2 × ULN and ≤ 35% direct
- creatinine ≤ 2.0 mg/dl or 177µmol/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.

5.1.11 Left ventricular cardiac ejection fraction (LVEF) within normal institutional limits as measured by echocardiogram.

5.1.12 In case of patients of child bearing potential:

- Negative pregnancy test (minimum sensitivity 25 IU/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.

5.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for randomization:

5.2.1 History of hypersensitivity reactions attributed to compounds of similar chemical or biological composition to lapatinib.

5.2.2 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).

5.2.3 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.

5.2.4 Adverse events due to prior anticancer therapy which are > Grade 1 (NCI CTCAE) and therapeutically relevant at time of randomization.

5.2.5 Anti-retroviral therapy due to HIV infection.

5.2.6 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).

5.2.7 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.

5.2.8 Other malignant diseases within the last 3 years apart from CIN of the uterine cervix and skin basalioma.

5.2.9 Disease or condition which might restrain the ability to take or resorb 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, ulcerative colitis) and any other diseases significantly affecting gastrointestinal function as well as inability to swallow and retain oral medication for any other reason.

5.2.10 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.

5.2.11 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.

5.2.12 Life expectancy < 3 months.

5.2.13 Male patients.

5.2.14 Pregnancy or nursing.

5.2.15 Primary tumor or biopsies from metastatic sites or locoregional recurrences showing HER2-positivity.

5.2.16 Any prior treatment with anti-HER2 directed therapy.

6.0 PRE-TREATMENT EVALUATION

(cf. APPENDIX II – PATIENT EVALUATION FLOW SHEET)

In General
During the pre-treatment evaluation period there are **two visits**. The first visit is the Screening Visit; the second one is the Randomization Visit.
The **Screening Visit** is only performed for CTC count and assessment of HER2 status on CTC. Thus, it is avoided to bother the patient with detailed information on the whole study before the HER2 status on CTC is known. Blood sampling for CTC count and assessment of their HER2 status should be scheduled at least one week after last application of investigational agents of any type or anticancer therapy.
The **Randomization Visit** is only scheduled for a patient if the HER2 status on CTC is positive. It serves to perform the required baseline examinations, to check the in- and exclusion criteria and to randomize the patient to protocol treatment.
Corresponding to the arrangement of the visits, patient information and informed consent takes place in two steps (see section 16.4). The visits during the pre-treatment evaluation period are only performed if patients are left sufficient time to make their decision on study participation.
With the exception of quality of life assessments and the blood samplings for the examination of CTC and translational medical investigations all procedures planned in the pre-treatment period are part of the clinical routine usual in patients with metastasizing breast cancer.

*Actions Taken on **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 16.5 Data Protection)*

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 (***Screening Kit****)
  - If CTC count or HER2 status on CTC is negative study participation is terminated
  - 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.

*Actions Taken on **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.*** Please observe also the time intervals allowed for the results of several examinations (see table below). Results obtained before Randomization Visit may be employed if they meet the given 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 (see section 16.4 and 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 (see section 16.4 and 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 (see tables of section 8.2.1.).
- Physical examination.
- Vital signs (heart rate, blood pressure, body temperature), height and weight.
- Blood sampling for hematology and biochemistry (see also table below for parameters and allowed time intervals).
- Blood sampling for translational medical investigations with ***Analysis Kit*** only in patient who have given informed consent – part 3.
- Serum or urine pregnancy test (see also table below for parameters and allowed time intervals).
- Tumor evaluation (see section 10.2.1 for examinations to be done and table below for allowed time intervals).
- Cardiac investigations (see table below examinations to be done and allowed time intervals).
- Quality of life assessment (see table below questionnaires and allowed time intervals).
- 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.
    Patients who are excluded from the study and who consent in additional assessment will be monitored during their course of disease as part of their routine treatment in order to gain further information about the impact of CTC detection on disease progression.
  - If the patient meets all inclusion criteria and none of the exclusion criteria, she is eligible for randomization according to section 7.0 of the protocol and for protocol treatment according to section 8 of the protocol.
- Dispense of lapatinib only for patients randomized to lapatinib treatment immediately prior to start of randomized protocol treatment.
- Randomized protocol treatment (i.e. standard chemo- or endocrine therapy +/- lapatinib) starts for eligible patients within one week of randomization.
- Assessment of adverse events.

Table: Information on special investigations during Pre-Treatment Period

Investigation		**Time interval before randomization**
Blood Sampling with Screening Kit (Screening Visit) for CTC assessment	- Total number per 7,5 mL	3 weeks (Results must be available prior to IC part 2 and prior to start of Randomization Visit)
	- HER2 status	
Hematology	- Hemoglobin - Hematocrit - Red blood cell count - Differential white blood cell count - Platelet count	7 days

Biochemistry	- Total and direct bilirubin - ALT - AST - Serum creatinine - Albumin - BUN or urea - Sodium, potassium, calcium	7 days
Coagulation	- INR - aPTT or PTT	7 days
Serum or urine pregnancy test	Patients of child bearing potential only, minimum sensitivity: 25 U/L	7 days
Tumor evaluation (see section 10.2.1)	- Mandatory imaging	6 weeks
	- Other imaging as necessary to document all sites of disease	6 weeks
	- Clinical lesion status	6 weeks
	- Tumor markers (mandatory: CA15-3; optional: CEA, CA125)	6 weeks
Cardiac investigations	- 12-lead ECG - UCG (including LVEF assessment)	3 weeks
Quality of life questionnaires	- EORTC QLQ-C30 - EORTC QLQ-BR23	1 week

7.0 RANDOMIZATION PROCEDURE

If a patient meets all inclusion criteria and none of the exclusion criteria at Randomization Visit she will be randomized.

Online randomization is possible 24 hours a day. After the registration form of the eCRF has been saved, the randomization result is notified immediately by an automatically generated fax to the investigator.

The randomization lists will be kept in safe and confidential custody at Alcedis GmbH.

8.0 TREATMENT PLAN

8.1 General

Protocol treatment: During the randomized treatment period all patients receive a standard chemo- or endocrine therapy (see section 8.3) combined with or not combined with the IMP lapatinib (see section 8.2).

During the follow-up period treatment is at the discretion of the responsible investigator (see section 12.1.3 "Therapy after End of Protocol Treatment").

8.1.1 *Dose Delays and Dose Modifications*

Dose reductions or delays will be considered for the stand chemo- or endocrine treatment and lapatinib and may occur independently. For detailed information on dose adjustment during therapy with lapatinib please refer to section 8.2.2.

Due to the wide spectrum of feasible antineoplastic therapy +/- lapatinib combinations dose reductions and delays of standard chemo- or endocrine treatment should follow general GCP criteria for the application of antineoplastic drugs *[Repetto 2003, NCCN-Guidelines www.nccn.org]* and should be made according to the SPC and/or investigator's brochure. The latest versions of the SPCs ("Fachinformation" according to German Drug Law) of the standard antineoplastic therapy will be provided on the DETECT III website. The Detect III study office in Ulm (Universitätsfrauenklinik Ulm, Studienzentrale, Prittwitzstr. 43, 89075 Ulm, Tel: 0731/500 58521, Fax: 0731/500 58526, Email: studienzentrale.ufk@uniklinik-ulm.de) can be contacted.

Subjects who require permanent discontinuation of one of the products due to unacceptable toxicities may switch to another treatment regime of the standard chemo- or endocrine treatment if medically reasonable. The patient remains in the arm that she was randomized to: +/- lapatinib.

The antineoplastic treatment of a patient can be postponed for up to 2 weeks to allow resolution of toxicity. The investigator must consult the DETECT III Study Office prior continuing therapy for any patient requiring a delay of study treatment of more than two weeks for any reason.

All patients who require permanent discontinuation of both lapatinib and the antineoplastic product in a given treatment combination will be withdrawn from the treatment intervention schedule (start of the 2-year follow-up period).

8.2 Treatment with lapatinib

8.2.1 *Drug Dispense, Administration and Treatment Regimens*

Lapatinib is only administered to patients randomized to a treatment with lapatinib in addition to a standard chemo- or endocrine therapy.

On Randomization Visit eligible patients are dispensed a bottle containing 90 tablets of lapatinib. On the following visits patients are provided with further bottles so that supply is assured to last until the planned next visit at the study site.

Patients take their first dose of lapatinib within one week after randomization. They are instructed to take their subsequent doses of lapatinib once daily at approximately the same time each day and at least 1 hour before a meal. Furthermore, patients are informed about the following:

- Lapatinib may also be administered as a suspension in water. Details are explained in section 3.1.7.
- If vomiting occurs shortly after the lapatinib tablets have been swallowed, the dose should be replaced only if all of the tablets taken are intact and can be seen and counted. Otherwise, the next dose should be taken the following day, as per schedule. Doses once missed must not be taken at a later point in time.
- Lapatinib should NOT be taken with grapefruit or grapefruit juice. For the duration of treatment with lapatinib patients are not allowed to eat grapefruit or to drink grapefruit juice.

The daily dose of lapatinib depends on the chosen standard chemo- or endocrine therapy (see section 8.3). Only dose combinations are allowed that are either approved (see SPC of Tyverb® 250 mg tablets) or that have been

investigated in prior clinical trials (see below table 8.2.1.a). The recommended treatment regimens can be found in the table 8.2.1.b.
In patients with hormone-receptor positive breast cancer treatment with aromatase inhibitors may be started / continued if chemotherapy has been paused or finished.

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 (see section 8.2.2).

In any case, the maximum daily dose is 1500 mg, the minimum daily dose is 750 mg. Tablets of lapatinib are available in a strength of 250 mg. To achieve the daily dose required a respective number of tablets is to be swallowed, e.g. 5 tablets if the daily dose is 1250 mg lapatinib or 6 tablets if the daily dose is 1500 mg lapatinib.

Table 8.2.1.a: Dose combinations of lapatinib with standard chemo- or endocrine therapy investigated in prior clinical trials

Lapatinib (Daily Dose) + Monochemotherapy (Daily Dose)	
lapatinib (1000-1500 mg) + docetaxel (50-75 mg/m²)	*[LoRusso 2008] [Bonnefoi 2008]*
lapatinib (1500 mg) + paclitaxel (175 mg/m²) lapatinib (1500 mg) + paclitaxel (80 mg/m²)	*[Di Leo 2008] [Guan 2010]*
lapatinib (1250 mg) + capecitabine (2000 mg/m²)	*[Geyer 2006] [Cameron 2008] [SPC of Tyverb® 250mg tablets]*
lapatinib (750-1250 mg) + vinorelbine p.o. (50 mg/m²)	*[Lu 2010] [Chew 2007] [Brain 2009]*
lapatinib (1250 mg) + NPLD (60 mg/m^2)	*[Anton2010] [Cortes 2009] [Theodoulou 2009] [Venturini 2010]*
Lapatinib + Monoendocrine Therapy (Daily Dose)	
lapatinib (1500 mg) + letrozole (2,5 mg) lapatinib (1500 mg) + aromatase inhibitors as recommended	*[Johnston 2009] [SPC of Tyverb® + SPCs of Aromatase Inhibitors]*

Table 8.2.1.b: Recommended treatment regimens

Lapatinib + Monochemotherapy	**Recommended treatment regimen**
lapatinib + docetaxel	Daily lapatinib 1250 mg + docetaxel 75 mg/m² 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 according to institutional standards.
lapatinib + paclitaxel	Daily lapatinib 1500 mg + paclitaxel 80 mg/m^2/weekly, or daily lapatinib 1500 mg + paclitaxel 175 mg/m² 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/m² 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/m² 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/m² 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

*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.

8.2.2 *Dose Adjustments*

Dose increase / Dose delay
In patients who were not treated with aromatase inhibitors and who did not require dose reduction during standard chemo- or endocrine therapy, lapatinib is increased to 1500 mg on the first regular visit after the last cycle of standard therapy. In case of persistent adverse reactions to standard therapy and in case of any other conditions contradicting dose escalation, it may be postponed at the investigator's discretion.

Dose reduction
Doses may be held or reduced for hematologic (see section 8.2.3) and other adverse events (see section 8.2.4). Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Once dose is reduced due to adverse events, patients should not be re-challenged to a higher dose level.

The major toxic effects of lapatinib which limit dose are nausea, vomiting, diarrhea, rash and fatigue. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

The lapatinib dose will be decreased according to the schedule displayed in the following table:

Table: Lapatinib Dose Reduction Schedule

Starting Dose (mg)	1st Reduction (mg)	2nd Reduction (mg)*	3rd Reduction (mg)*	4th Reduction (mg)*
1500	1250	1000	750	discontinue
1250	1000	750	discontinue	NA

*more than one dose reduction is permitted only in combinations with taxanes (due to possible PK interactions between taxanes and lapatinib leading to AUC increases for both drugs as demonstrated for the combination of paclitaxel and lapatinib by Crown et al. 2007 and Jones et al. 2004).

A dose of 750 mg represents the lowest dose that a patient can receive.

8.2.3 *Hematologic Adverse Events*

Absolute Neutrophils ($x10^9$/L)		Platelets ($x10^9$/L)	Lapatinib Dose Management
≥ 1.0	and	≥ 50	No dose change
< 1.0	and/or	< 50	• Hold lapatinib • If recovery of hematologic values within 14 days resume treatment at the same dose level • If no recovery of hematologic values within 14 days discontinue lapatinib permanently

8.2.4 *Non-hematologic Adverse Events*

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE) (APPENDIX IV – NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 4.03 (CTCAE)).

Skin Adverse Events:
A papulopustular rash is the most commonly observed skin adverse event for lapatinib. Such rash frequently improves with an unchanged, uninterrupted dose of lapatinib therapy. Severe skin AEs (CTC Grade 3 or more) associated with lapatinib are rare (1-3%). In general, patients with poorly tolerated skin toxicities may be successfully managed by providing a brief (up to 14 days) therapy interruption and resuming lapatinib at the same dose. In some cases, the rash may improve without the need for interrupting therapy with lapatinib.

Subjects should be encouraged to avoid exposure to sunlight. Broad spectrum sunscreens (containing titanium dioxide or zinc oxide) with a SPF of at least 15 should be applied.

A variety of agents can be used to manage skin reactions. These include mild-to-moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines and immunomodulators, as well as moisturizers.

There is no standard treatment, known or established, that is proven effective for drug-related skin rashes or changes due to lapatinib. The need for oral or topical antibiotics and topical steroids is a clinical decision of the investigator and, if indicated, a dermatology consultation. Oral retinoids are not recommended because of theoretical concerns about negatively affecting the lapatinib mechanism of action and topical steroids result in irritation/severe dryness. Oral steroids may be used for a short treatment course (maximum of 14 days) which may help patients to remain on study therapy. Upon consultation with a dermatologist, other treatment options may exist for difficult to treat/unresponsive skin toxicities.

The decision to administer, delay, dose-reduce or discontinue lapatinib due to skin adverse events is as follows:

Adverse Event	CTCAE Grade	Guideline for management	Lapatinib dose modification
Skin adverse Events	1	No intervention	None
	2	Any of the following as appropriate: oral or topical antibiotics, topical steroids, oral steroids (short course)	None*
	3		Hold until recovery to ≤ grade 1** If this is the first occurrence, resume at the same dose; if this constitutes recurrence, resume at 1 dose level lower
	4	As clinically appropriate	Discontinue lapatinib

* if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1** and then resume at the same dose; if dose has been previously held for grade 2 skin toxicity and grade 2 symptoms recur, hold dose until recovery to ≤ grade 1** and then resume at 1 dose level lower

** maximum hold for 14 days; if no recovery to ≤ grade 1 after 14 days, discontinue lapatinib

Diarrhea:
Experience thus far suggests that when lapatinib is used as monotherapy most diarrhea is uncomplicated NCI CTCAE Grade 1 or 2. In rare cases, diarrhea can be debilitating, and potentially life threatening with dehydration, renal insufficiency, and electrolyte imbalances.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea *[Benson 2004]*. The ASCO Management Guidelines *[Benson 2004]* for uncomplicated diarrhea (CTCAE Grade 1 or 2) and for complicated diarrhea (CTCAE Grade 3 or 4 diarrhea or Grade 1 or 2 with complicating features like moderate to severe cramping, nausea/vomiting ≥ Grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, dehydration) are described in APPENDIX IX – DIARRHEA MANAGEMENT GUIDELINES.

The definitions of diarrhea, uncomplicated and complicated diarrhea as well as detailed information about anti-diarrhea medications, supportive care and the decision to administer, delay, reduce or discontinue lapatinib due to diarrhea is found in APPENDIX IX – DIARRHEA MANAGEMENT GUIDELINES.

Adverse Event	CTCAE Grade	Diarrhea Management	Lapatinib dose modification
		(See APPENDIX IX – DIARRHEA MANAGEMENT GUIDELINES)	
Diarrhea	1	Follow Diarrhea Management Guidelines for *uncomplicated* diarrhea, A) I.	None
		In case of complicating features follow Diarrhea Management Guidelines for *complicated* diarrhea, B) I.	Hold lapatinib and chemotherapy (if applicable) until symptoms resolve to ≤grade 1 (without complicating features) and reintroduce lapatinib at a reduced dose (unless dose had been reduced to 750 mg). Consider a dose reduction for chemotherapy (if applicable).
	2	Follow Diarrhea Management Guidelines for *uncomplicated* diarrhea, A) II.	None
		In case of complicating features follow Diarrhea Management Guidelines for *complicated* diarrhea, B) I.	Hold lapatinib until symptoms resolve to ≤grade 1 (without complicating features) and reintroduce lapatinib at a reduced dose (unless dose had been reduced to 750 mg). Consider a dose reduction for chemotherapy (if applicable).
		In case of *persistent* (≥ 3days/72hrs) grade 2 Diarrhea follow Diarrhea Management Guidelines, A) III.	Hold lapatinib and chemotherapy (if applicable) until diarrhea resolves (<grade 1/return to baseline bowel pattern). After diarrhea resolves (<grade 1/return to baseline bowel pattern), resume treatment with lapatinib and chemotherapy (if applicable).
		In case of *recurrent* diarrhea (> 1 occurrence of grade 2 diarrhea) follow Diarrhea Management Guidelines, A) IV.	Once the 2nd occurrence of grade 2 diarrhea resolves to ≤grade 1, consider reducing the dose of lapatinib by 250mg or 1 tablet, unless the lapatinib dose already had been reduced to 750 mg. No further dose reduction is recommended for subjects taking lapatinib at 750 mg. Consider a dose reduction for chemotherapy (if applicable).

	3	Follow Diarrhea Management Guidelines for *complicated* diarrhea B) I.	Hold lapatinib and chemotherapy (if applicable) until symptoms resolve to ≤grade 1 (without complicating features) and re-introduce lapatinib at a reduced dose (unless dose had been reduced to 750 mg). Consider a dose reduction for chemotherapy (if applicable).
	4	Follow Diarrhea Management Guidelines for *complicated* diarrhea, B) II.	Hold treatment with lapatinib, hold chemotherapy or other concurrent anticancer therapy (if applicable). Evaluate the patient case history when deciding on the re-initiation of study treatment, including dose modifications, following resolution of diarrhea (≤grade 1).

Note: Patients should be educated on signs and symptoms of diarrhea with instructions to report to any changes in bowel patterns to the physician. *Stand-by prophylaxis with loperamide* is recommended for patients treated with lapatinib. It is strongly recommended to give subjects receiving lapatinib-based therapy a prescription of loperamide with instructions to start loperamide at the onset of diarrhea as per the recommendations outlined below. However, loperamide should not be taken prophylactically to prevent diarrhea.

Interstitial Pneumonitis:
Interstitial pneumonitis has been reported in subjects taking compounds that inhibit ErbB1.

Adverse Event	Guideline for management	Lapatinib dose modification
Signs and symptoms of Interstitial Pneumonitis	Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated. If NCI CTCAE grade ≥3 report as SAE (cf. section 11.2)	Hold pending diagnosis
		Permanently discontinue if interstitial pneumonitis diagnosis is confirmed.

Cardiac Adverse Events (including LVEF decrease):
Cardiovascular events have been seen in subjects taking other compounds that inhibit ErbB2 when used in combination with or following anthracyclines. In case or suspicion of a cardiac adverse event the results of both, the LVEF measurement and the assessment of the NYHA functional status (see APPENDIX VII – NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE) must be available prior to deciding subsequent administration of lapatinib. Specifically, the decision to administer, delay or discontinue lapatinib is as follows:

Asymptomatic cardiac events: Subjects who have a ≥ 20% decrease in left ventricular cardiac ejection fraction relative to baseline, and the ejection fraction is below the institution's lower limit of normal, should have a repeat evaluation of ejection fraction 1-2 weeks later while still receiving investigational product. ▪ If the repeat ejection fraction evaluation confirms a ≥ 20% decrease in left ventricular cardiac ejection fraction, and the ejection fraction is below the institution's lower limit of normal, then investigational product should be temporarily discontinued. ▪ If the left ventricular ejection fraction recovers during the next 3 weeks, after consultation and approval of the medical monitor, the subject may be restarted on investigational product at a reduced dose. For such subjects, monitoring of left ventricular ejection fraction will then be performed 2 weeks and 4 weeks after rechallenge, and then every 4 weeks thereafter. ▪ If repeat ejection fraction evaluation still shows a decrease ≥ 20% in left ventricular ejection fraction relative to baseline, and the value is below the institution's lower limit of normal, then the subject should be withdrawn from investigational product.
Symptomatic cardiac events: Subjects with a NCI CTCAE grade 3 or 4 LVEF relative decrease must be withdrawn from study medication.
Cardiological consultation In general, it is strongly recommended that patients who have symptomatic decreases in LVEF or those

who meet the criteria for stopping treatment seek cardiological consultation for advice on potential treatment for their cardiac dysfunction. Furthermore, in patients who permanently discontinue lapatinib due to cardiac toxicity, cardiac evaluations should be performed as clinically indicated, ideally every 4 weeks for at least 16 weeks or until resolution.

Cardiac dysfunction which exhibits any signs or symptoms of deterioration in left ventricular cardiac function that are ≥grade 3 (NCI CTCAE) or a ≥20% decrease in left ventricular cardiac ejection fraction relative to baseline which is below the institution's lower limit of normal is reported as serious adverse event.

Hepatic Toxicity:
Hepatotoxicity has occurred with the use of lapatinib. The changes most commonly seen are elevations in transaminases, but rarely severe hepatocellular damage may occur. Elevated liver enzymes usually return to baseline levels when lapatinib is stopped, but may rise again on re-exposure.

After each assessment of blood chemistry (cf. section 9.1) the decision to continue, reduce, hold or discontinue treatment with lapatinib is made as follows:

- If a subject experiences **ALT >3 × ULN, total bilirubin >2.0 × ULN, and bilirubin fraction >25%**, then the following actions must be taken:
  - immediately and permanently discontinue lapatinib;
  - perform the follow-up assessments specified in the table below and document results on the liver follow-up assessment page of the eCRF;
  - in addition to the liver event follow up assessments mentioned in the table below, the following are suggested: specialist or hepatology consultation; anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies; and liver imaging and/or liver biopsy to evaluate liver disease;
  - promptly report the event as **SAE** as described in section 11.2;
  - monitor every week until liver chemistries (cf. table below) resolve, stabilize or return to within baseline values and report results in the eCRF.

- If **total bilirubin is ≤ 2.0 × ULN or bilirubin fraction ≤35%**, but a subject experiences:
  - **ALT >8 × ULN or**
  - **ALT >5 × ULN persisting for ≥2 weeks** (retest within 3 days from the first occurrence and then weekly to determine if ALT elevation persists) **or**
  - **ALT >3 × ULN with signs or symptoms of hepatitis or hypersensitivity** (the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia),

  then
  - hold lapatinib for 2 weeks,
  - repeat liver chemistry testing in 2 weeks, and
  - then call the medical monitor to discuss the possibility of re-challenging with lapatinib. If the treatment is exhibiting efficacy and the subject wants to continue for potential benefit of lapatinib, this is considered when deciding on re-challenge.
  - If re-challenged, start lapatinib at the agreed upon reduced dose.
  - If not re-challenged report event as SAE (cf. section 11.2)
  - Liver chemistries and aforementioned signs and symptoms are monitored at a minimum of every 2 weeks until resolution, stabilization, or a return to baseline values, at which point monitoring should be continued per protocol.

- If a subject experiences **ALT >3 × ULN but <5 × ULN** and if **total bilirubin ≤2 × ULN or bilirubin fraction ≤35%, without signs or symptoms of hepatitis or hypersensitivity**, then the following actions should be taken:
  - Continue lapatinib and monitor liver chemistries weekly;
  - if ALT >3 x ULN for >4 weeks (and the patient does not meet one of the aforementioned liver stopping criteria), discontinue treatment and report the event as SAE (cf. section 11.2);
  - if at any time the subject meets any of the aforementioned liver chemistry stopping criteria, then proceed as described above;

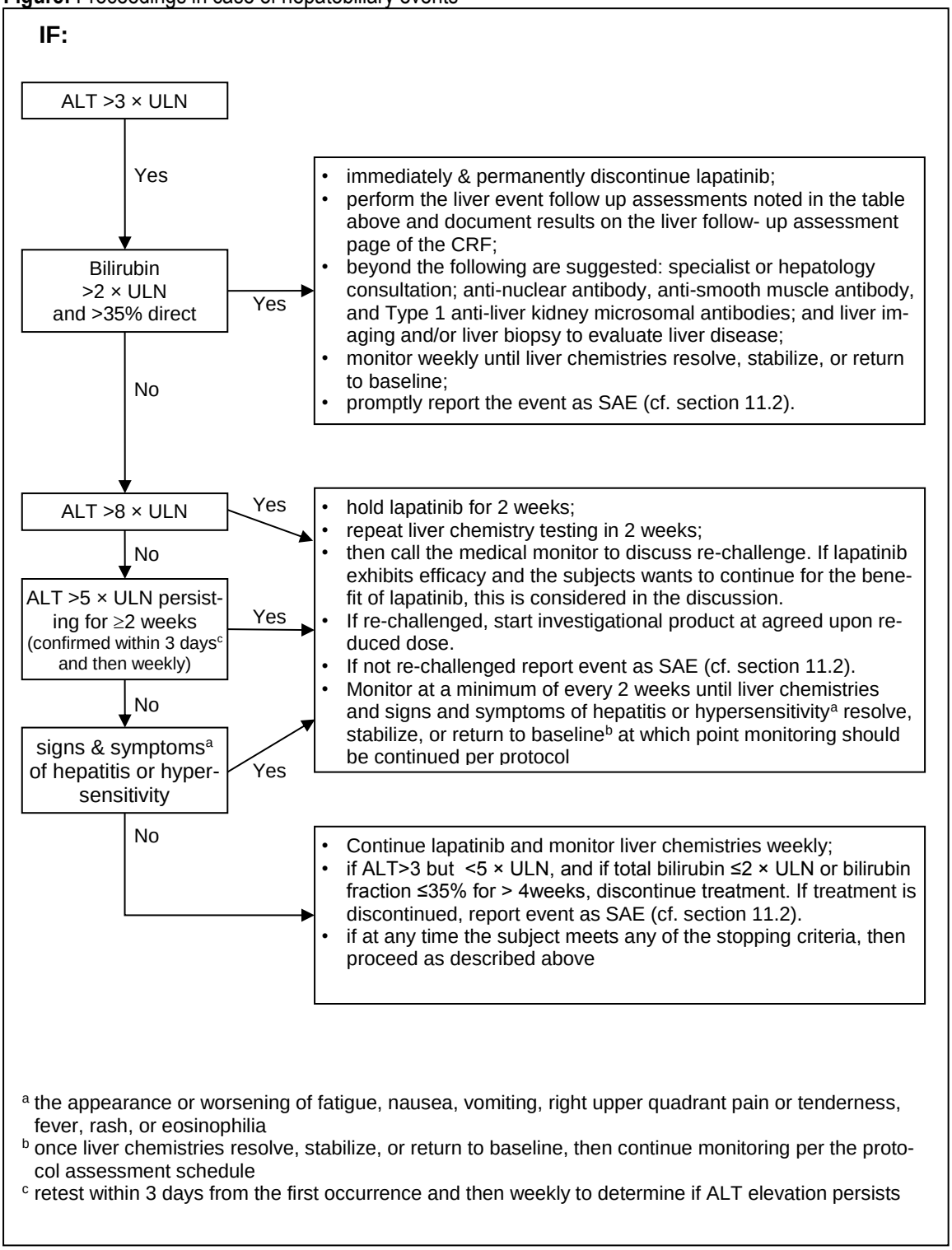
Table: Follow-up assessments in case of hepatobiliary events

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody (if subject resides or has travelled outside Europe in past 3 months);
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Complete blood count with differential to assess eosinophilia;
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form;
- Record alcohol use on the liver event alcohol intake case report form.

Table: Parameters required for liver event monitoring

- Total and direct bilirubin
- ALT
- AST

Figure: Proceedings in case of hepatobiliary events



[a] the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

[b] once liver chemistries resolve, stabilize, or return to baseline, then continue monitoring per the protocol assessment schedule

[c] retest within 3 days from the first occurrence and then weekly to determine if ALT elevation persists

Other Non-hematologic Adverse Events (not specifically addressed above):

CTCAE grade	Management / Lapatinib Next Dose
≤ grade 2	Symptomatic care – no change in dose. If prolonged duration (≥ 14 days) of grade 2 adverse event despite symptomatic treatment, then hold lapatinib until ≤ grade 1* and resume at same dose. If grade 2 adverse event recurs OR if the patient finds the symptoms unacceptable, hold lapatinib until recovery to ≤ grade 1 and then resume at 1 dose level lower.
grade 3	Hold for up to 14 days* until ≤ grade 1, then resume at 1 dose level lower
grade 4	Off lapatinib therapy
* Patients requiring a delay of > 14 days should discontinue lapatinib	

If lapatinib is discontinued the event is reported as SAE (cf. section 11.2).

8.2.5 *Duration of Lapatinib Therapy*

Duration of lapatinib therapy is 12 months (see section 12.1.2), unless disease progression or other criteria for premature discontinuation (see section 12.1.1) 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).

Treatment after completion or premature discontinuation of lapatinib (i.e. treatment in the follow-up period) is described in section 12.1.3.

8.2.6 *Patient Compliance*

Compliance with daily lapatinib is very important to the conclusions of this study. To assess treatment compliance patients are asked to present all tablets not yet used on every visit to the study site. At the end of the treatment period patients must return all unused tablets. Patients are instructed to notify the investigator of any missed doses.

The investigator will make tablet counts at each patient visit during treatment. The tablet counts are to be documented in the eCRF. Dates of missed doses are also to be recorded on the eCRF.

8.3 Standard Chemo- or Endocrine Therapy

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).
Patients who will be treated with aromatase inhibitors should undergo a baseline bone density scan before treatment.

Monochemotherapy	**Recommended Dosing**
Docetaxel	75 mg/m² i.v. d1 q3w
Paclitaxel	80 mg/m² i.v. weekly or 175 mg/m² d1 q3w
Capecitabine	2 x 1000 mg/m² p.o. d1-14 q3w
Vinorelbine	50 mg/m² p.o.* d1+d8 q3w (dose escalation according to patient's tolerance)
NPLD	60 mg/m² 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).

Duration of standard chemo- or endocrine therapy is described into detail in section 12.1.2. and 12.1.1.

Therapy after randomized treatment period (i.e. treatment in the follow-up period) is at the discretion of the investigator as described in section 12.1.3.

8.4 Concomitant Therapy

The electronic case report forms (eCRFs) will capture the use of all drugs, over-the-counter medications, or alternative therapies including herbal supplements, taken by the patient from 2 weeks prior to randomization and during the Follow up assessments.

8.4.1 *Permitted*

- Use of supportive therapy for protocol treatment induced toxicities is permitted.
- Patients should receive full supportive care and palliative care (e.g. pain control) as clinically indicated during the trial, including transfusion of blood products, and treatment with antibiotics, antiemetics, antidiarrheals and analgesics when appropriate, *with the exception of* the therapies mentioned in section 8.4.2.
- Stand-by prophylaxis with *loperamide* is recommended for patients treated with lapatinib. At the time of starting lapatinib, all patients should be given a prescription for loperamide or analogue and be advised to keep the prescription/medication with them at all times.
- Primary prophylaxis with lipegfilgrastim (Lonquex®) is recommended to be administered with docetaxel and lapatinib combination therapy. Otherwise, G-CSF, GM-CSF and other hematopoietic growth factors may not be used as a substitute for a scheduled dose reduction for standard chemotherapy regimens unless this is the center's standard practice; however, in case of severe neutropenia or febrile neutropenia, G-CSF support with lipegfilgrastim may be used in the following cycles if a dose reduction is not considered as appropriate. Erythropoietin may be used if clinically indicated and as per institutional standards. Use of growth factors must be documented on the case report forms

Palliative radiotherapy is permitted. It should not be delivered to a target lesion. IF palliative radiotherapy is initiated, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out. No dose modification of study treatment is needed during palliative radiotherapy.

8.4.2 *Not Permitted*

- Anti-cancer treatment other than protocol therapy:
  Must not be given until disease progression.

- *Cytochrome P450 inhibitors or inducers:*
  Lapatinib is primarily metabolized by liver enzymes, particularly CYP3A4. Co-administration of potent inhibitors or inducers of this enzyme can result in significant changes in exposure to lapatinib. For this reason, use of CYP3A4 inhibitors and inducers is not permitted before or during the study:
  - Inhibitors – prohibited 7 days before dosing (6 months for amiodarone) and during protocol treatment
  - Inducers – prohibited 14 days before dosing and during protocol treatment

- *Glucocorticosteroids (oral):*
  Oral glucocorticosteroid use is not allowed during lapatinib treatment unless absolutely necessary (e.g. for treatment of adverse events or protocol-required premedications) or short-term (up to 2 weeks) because many such steroids effectively lower lapatinib exposure through CYP3A4 interactions.

- *Substrates of CYP2C8:*
  Since lapatinib is an inhibitor of CYP2C8, agents as repaglinide which are substrates of this enzyme and of low therapeutic range must not be administered during treatment with lapatinib.

- *Substrates of the transport proteins proteins Pgp, BCRP and OATP1B1:*
  In vitro lapatinib was found to inhibit the transport proteins Pgp, BCRP and OATP1B1. Therefore cardiac glycosides and other substrates of one of these proteins like rosuvastatine are not permitted during treatment with lapatinib.

- *Antacids:*
  Antacids are not allowed one hour before and after dosing.

- *Herbal and dietary supplements and traditional Chinese medicines:*
  Because the composition, pharmacokinetics and metabolism of many herbal supplements are unknown, concurrent use of all herbal supplements is prohibited during protocol treatment.

APPENDIX VI – PROHIBITED MEDICATIONS provides a comprehensive list of prohibited therapies.

9.0 EVALUATION

(cf. APPENDIX II – PATIENT EVALUATION FLOW SHEET)

9.1 Evaluation During Randomized Treatment Period

In General
With the exception of the blood samplings for circulating tumor cells and translational medical investigations, assessment of adverse events, survival, quality of life and tablet count all procedures performed during randomized treatment period are part of the clinical routine usual in metastatic breast cancer.

Scheduled Control Visits
For patients with standard chemotherapy +/- lapatinib there is a visit every three *or* four weeks (21/28±3 days) depending on chemotherapy treatment schedule during randomized treatment period. For patients with standard endocrine therapy +/- lapatinib there is a visit every three weeks (21±3 days). The date of each Control Visit is not determined with respect to the preceding one but with regard to time since first dose of protocol treatment (21/28±3, 42/56±3, etc. days after first dose). On each visit the following procedures are carried out:

- Assessment of vital signs (heart rate, blood pressure, temperature)
- Physical examination
- Assessment of adverse events (see section 11)
- Documentation of protocol treatment (standard therapy +/-lapatinib therapy)
- Tablet count, further supply of lapatinib if necessary
- Assessment of concomitant medication (denomination, start date/end date, specification if ongoing, dosage, route)
- Blood sampling for hematology and chemistry. Analyses are to include the parameters given in the table below.
- Assessment of quality of life by means of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires
- Assessment of pain intensity by use of the Numeric Rating Scale (NRS)
- Assessment of survival

Table: Standard hematology and biochemistry

Hematology	- Hemoglobin - Hematocrit - Red blood cell count - Differential white blood cell count - Platelet count
Biochemistry	- Total and direct bilirubin - ALT - AST - Albumin - Serum creatinine - BUN or urea - Sodium, potassium, calcium

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 according to section 10.2.1
- 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

Assessments independent of scheduled Control Visits

- Hematology and chemistry assessments as well as measurements of LVEF are carried out whenever clinically indicated and when monitoring toxicities in particular (cf. section 8.2). Measurements of LVEF and the parameters listed in the table above are reported on the eCRF LVEF and laboratory pages.
- Adverse events (cf. section 10) are assessed on each patient visit to the study site whether scheduled or not.

Conclusion Visit of the Randomized treatment period
The conclusion visit of the randomized treatment period is performed
- as soon as possible in case of disease progression
- as soon as possible in case of other criteria for premature discontinuation of protocol treatment (as defined in section 12.1.1.)
- 12 months after randomization in case of no tumor progression or other criteria for premature discontinuation of protocol treatment occur (see below the "note for clarification")

The following actions are taken:
- Assessment of vital signs (heart rate, blood pressure and body temperature),
- Physical examination,
- Assessment of adverse events (cf. section 11),
- Assessment of concomitant medication,
- Documentation of end of protocol treatment (standard therapy +/-lapatinib therapy) and of planned therapy after end of protocol treatment,
- Blood sampling for hematology and chemistry. Analyses are to include the parameters given in the table above,
- 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,
- UCG (including LVEF assessment),
- Assessment of quality of life by means of the EORTC QLQ-C30 and the EORTC QLQ-BR23 questionnaires,
- Collection of unused lapatinib, tablet count,
- Assessment of survival.
- Reminding the patient of the planned follow-up procedures.

Protocol treatment (i.e. standard chemo- or endocrine therapy with or without lapatinib) ends with this visit and subsequent therapy is as described in section 12.1.3 "Therapy after end of protocol treatment".

Note for clarification
For patients of the control group whose protocol treatment (standard therapy without lapatinib) has a *planned* duration of *less than 12 months* the following applies:
- In case the standard therapy regimen can be completed as scheduled (without need for premature discontinuation due to tumor progression or other criteria) these patients *remain in the "randomized treatment period"* after completion of standard therapy and the assessments of the "*control visits"* will be performed as described above. This procedure will be continued until the patients present with tumor progression or – otherwise – until 12 months after randomization. In both cases the "conclusion visit of the randomized treatment period" will be performed and subsequently the "follow-up period" (as described in section 9.2.) will start.

9.2 Evaluation During Follow-Up Period (After Randomized Treatment Period)

Follow-up procedures are study specific and not part of the usual routine in case of metastasizing breast cancer.

Between two and four weeks after conclusion visit of the randomized treatment period and then at least every three months the following is assessed during routine visits in the clinical trial center or via telephone call:
- adverse events which are ≥grade 3 NCI CTCAE and/or serious
- concomitant medication
- survival

Therapy during Follow-Up Period is as described in section 12.1.3 "Therapy after end of protocol treatment".

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

For definition of "target lesion", "progressive disease" (PD), "partial response "(PR) and "complete response (CR) please refer to section 10.2.1

10.1.1 *Progression Free Survival (PFS)*: PFS is defined as the time interval between the date of randomization and the date of PD or death from any cause, whichever comes first.

10.1.2 *Overall Survival*: Overall survival is defined as the time interval between the date of randomization and the date of death from any cause.

10.1.3 *Overall Response Rate*: The overall objective response rate applies only to patients with whom target lesions were defined at baseline. It is defined as the rate of CR and PR.

10.1.4 *Clinical Benefit Rate*: The clinical benefit rate applies to all patients. It is defined as the sum of the total number of patients with whom target lesions were defined and who achieve a complete or partial response and those patients who had stable disease for at least 6 months divided by the total number of patients in a treatment group.

10.2 Evaluation of Endpoints

10.2.1 *Tumor evaluation (Evaluation of response and progression of metastatic disease)*

Examinations regarding tumor evaluation:

On each tumor evaluation (during pre-treatment period and regularly every 8 to 12 weeks during randomized treatment period) the same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. The following examinations have to be done:

- Clinical assessment of all lesions is mandatory. For tumor evaluation clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter. Documentation by color photography including a ruler is suggested.
- Imaging is performed as follows:
  - CT, MRI (Chest, Abdomen, Pelvis): CT is the preferred method of tumor evaluation. In certain circumstances MRI may be used instead, for details please refer to the RECIST-Guideline *[Eisenhauer 2009]*.
  - CT, MRI (Head): A CT/MRI of the head is performed only if clinically indicated or if subject has a history of central nervous system metastases.
  - Chest X-Ray: Chest X-Ray measurement of lesions is feasible, but not preferable. Lesions on chest x-ray are only acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. In case of performing CT-Scans there is no additional Chest X-Ray assessment necessary.
  - Bone Scan and PET: Are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions *[Eisenhauer 2009].*
  - Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised (described in greater detail in Appendix II of the RECIST-guideline *[Eisenhauer 2009]*). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
  - PET/CT: Should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if the CT performed as a part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with i.v. and oral contrast) then the CT portion of the PET-CT can be used for RECIST measurements.
  - Additional imaging is to be performed for assessment of further known lesions or if required by clinical suspicion of new lesions.
- Tumor markers are assessed on each tumor evaluation: CA15-3 is mandatory, CA125 and CEA are optional.
- Endoscopy, laparoscopy: These techniques must not be used for objective tumor evaluation. However biopsies obtained may be used to confirm complete response or assess relapse after complete response
- Cytology: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Definitions and guidelines regarding tumor evaluation:

- At baseline during pretreatment period tumor lesions and/or lymph nodes are categorized measurable/non-measurable and target/non-target as follows:
  - Measurability:
    A lesion is considered measurable if the longest diameter in the plane of measurement is at least
    - 10 mm in case of CT scan
    - 10 mm caliper measurement in case of clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
    - 20 mm in case of X-ray

    Lymph nodes are considered pathologically enlarged and measurable if ≥ 15 mm in short axis when assessed by CT scan.

    Any other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to < 15 mm short axis) as well as truly non-measurable lesion are considered non-measurable. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural and pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

  - Target/non-target lesions:
    If on baseline tumor evaluation there are at least two measurable lesions a maximum of five in total and a maximum of two per organ are selected as target lesions. In case of lymph nodes the length of the short axis, in case of other lesions the longest diameter is recorded. Target lesions should be selected on the base of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should be those which lend themselves to reproducible repeated measurements. The sum of the lesion diameters (LD) assessed for all target lesions is calculated and reported as baseline sum LD. All other lesions are considered non-target and reported without diameter whether measurable or not.

- On the regular tumor evaluations during randomized treatment period, which are performed every 8 to 12 weeks or every 3 months in case of an endocrine treatment LD is re-assessed. All non-target lesions are reported "present", "absent" or "unequivocal progression
- Generally:
  - Response and progression of metastatic disease is evaluated using the international guidelines Version 1.1 proposed by the RECIST committee *[Eisenhauer 2009]*.
  - For detailed instruction on lesion measurements, follow-up of non-target lesions and special considerations regarding lymph nodes, bone lesions, cystic lesions, lesions not observed at baseline and lesions with prior radiologic treatment please refer to the **RECIST guideline Version 1.1** *[Eisenhauer 2009]*.

Assessment of tumor response:

Tumor response is assessed as follows:

- *Evaluation of target lesions:*

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest sum on study). In addition to the relative increase of 20% the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more lesions is also considered progression)
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

- *Evaluation of non-target lesions:*

  Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

  Non-CR/Non-PD: Persistence of one or more non-target lesions above normal limits

  Progressive Disease (PD): Unequivocal progression of existing non-target lesions

- *Evaluation of Overall Response:*

  From evaluations of target and non-target lesions and accounting for newly observed lesions Overall Response is assessed as described in the following tables:

Table: Evaluation of patients with target disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not at all evaluated	No	PR
SD	Non-PD or not at all evaluated	No	SD
Not at all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table: Evaluation of patients with non-target disease only

Non-Measurable Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not at all evaluated	No	Not evaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Data to be reported regarding tumor evaluations:

On each tumor evaluation the following data are reported (definitions see above):

- Concerning each lesion/lymph node:
  - Location
  - Measurable/non-measurable
  - Target/non-target
- Concerning non-target lesions: Present/absent/unequivocal progression
- Concerning target lesions only
  - Lesion diameter (LD) (short axis in case of lymph nodes, longest axis in other cases according to RECIST guidelines)
  - Sum of lesion diameters (LD) assessed for all target lesions
- Tumor marker level

Beyond, the following information is provided on tumor evaluations during randomized treatment period:

- Response of target lesion (CR, PR, PD, SD)
- Response of non-target lesion (Present/absent/unequivocal progression: CR, Non-CR/Non-PD, PD)

At conclusion of the randomized treatment period the following information is provided:

- Overall Response

10.2.2 *Evaluation of Circulating Tumor Cells (CTC)*

Count of CTC:

For counting CTCs are isolated by means of the CellSearch® Circulating Tumor Cell Kit (Veridex LLC, Raritan, USA).

Assessment of HER2 Status of Circulating Tumor Cells:

Blood samples will be collected into CellSave tubes (Veridex Inc.). The CellSearch Epithelial Cell Test (Veridex Inc.) will be applied for CTC enrichment and enumeration. The method has been described in detail elsewhere [*Riethdorf 2007*]. In brief, CTCs are captured from peripheral blood by anti-epithelial cell adhesion molecule (Ep-CAM)-antibody-bearing ferrofluid and subsequently identified by cytokeratin-positivity/negativity for the leukocyte common antigen CD45 and 4',6-diamidino-2-phenylindole (DAPI) staining to ensure the integrity of the nucleus. A blood sample is considered positive when at least one CTC is present based on the prognostically relevant cut-off as previously published [*Cristofanilli 2004, Budd 2006*]. HER2 expression of CTCs will be characterized within the CellSearch assay by addition of a fluorescein isothiocyanate (FITC)-labeled anti-HER2 antibody (CellSearch tumor phenotyping reagent HER2, Veridex Inc.), as described previously [*Hayes 2002, Meng 2004, Riethdorf 2010*]. The intensity of the HER2-specific immunofluorescence will be categorized into negative (0), weak (1+), moderate (2+), and strong (3+). CTCs are considered HER2 positive if at least one CTC has at least 1+ HER2 staining.

10.2.3 *Evaluation of Quality of Life*

The EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires are used (see APPENDIX V – QUALITY OF LIFE ASSESSMENTS). Data are analyzed according to the respective EORTC manuals.

10.2.4 *Evaluation of pain intensity*

To assess pain intensity a numeric rating scale is used (see APPENDIX XII – ASSESSMENT OF PAIN INTENSITY).

11.0 ADVERSE EVENT REPORTING

11.1 Definition, Collection and Recording of Adverse Events by the Investigator

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In particular this includes new findings or changes from baseline in laboratory test results or any other safety assessments (e.g. ECGs, radiological scans, vital signs assessments) felt to be clinically significant in the medical and scientific judgment of the investigator.

During randomized treatment period AEs are collected by the investigator at least on every visit of the patient at the study site, whether it is a scheduled study visit or not.

During the follow-up period (after conclusion of the randomized treatment period) only adverse events are collected by the investigator which are ≥ grade 3 NCI CTCAE and/or serious.

Every adverse event is followed up until it has subsided or stabilized.

On each AE the following data are raised and documented by the investigator in the respective electronic case report form:

- Diagnosis or each single symptom if diagnosis is not available,
- date and time of onset and end of AE,
- whether onset was after the first administration of study medication (yes/no),
- course (continuous / intermittent, if intermittent: number of episodes),
- whether the AE is a reportable serious adverse event (serious/ non-serious, for the definition of "reportable serious event" cf. section 1.3),
- intensity (grade 1 to 5 according to the NCI Common Terminology Criteria for Adverse events (CTCAE) version 4.03),
- causal relationship with investigational medicinal product (no (not related) / yes (reasonable possibility)),
- counter-measures (none/dose reduced/ drug withdrawn/other drug treatment/other measures),
- outcome (recovered/ recovering/ not recovered/ recovered with sequelae/fatal/ unknown),
- whether the AE is a change in liver-chemistry including ALT> 3 × ULN. If so, whether during the event bilirubin was >2.0 × ULN and bilirubin fraction was >35% simultaneously. If during the event total bilirubin and bilirubin fraction were not simultaneously >2.0 × ULN and >35% respectively, whether ALT was >8 × ULN, whether ALT was>5 × ULN persisting for 2 weeks or whether there were signs and symptoms of hepatitis.

To allow for a more appropriate evaluation of adverse events, toxicities due to previous anticancer medication which occurred before randomization are also reported specifying the kind of toxicity, start date, end date / specification if ongoing, and severity according to NCI CTCAE Version 4.03.

11.2 Definition, Collection and Expedited Reporting of Serious Adverse Events by the Investigator

A serious adverse event (SAE) is any adverse event that at any dose

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support for the purposes of decreasing hematological toxicity (e.g. GCSF), elective surgery and admissions for palliative or terminal care),
- results in persistent or significant disability or incapacity and/or
- is a congenital anomaly/birth defect.

Cardiovascular events have been seen in subjects taking other compounds that inhibit ErbB2 when used in combination with or following anthracyclines, and interstitial pneumonitis has been reported in subjects taking compounds that inhibit ErbB1. As a precaution, the following will be reported as a SAE:

- Cardiac dysfunction defined as any signs or symptoms of deterioration in left ventricular cardiac function that are ≥ grade 3 (NCI CTCAE) or a ≥ 20% decrease in left ventricular cardiac ejection fraction relative to baseline which is below the institution's lower limit of normal,

- any signs or symptoms of pneumonitis that are ≥ grade 3 (by the NCI CTCAE Version 4.03),

Furthermore, since hepatotoxicities are considered to be potential side effects of lapatinib, the following is considered and reported as SAE:

- ALT > 3 x ULN with total bilirubin > 2.0 x ULN (with direct bilirubin > 35%)
- any permanent discontinuation of lapatinib due to hepatotoxicity (see section 8.2.4).

The investigator shall report all serious adverse events (including serious adverse reactions and suspected serious adverse reactions) to the sponsor immediately (within 24 hours) after becoming aware of them. Each serious adverse event must be documented on the electronically available "**Serious adverse events report**" form. The completed form is automatically faxed (fax no. is filed automatically in the system) to the sponsor and Alcedis GmbH. In the event that electronic reporting is not possible, paper SAE forms in the investigator's file handed out at the beginning of the study are at the doctor's disposal for notification by conventional fax.

SPONSOR'S STUDY OFFICE:

Universitätsklinikum Ulm
Prittwitzstr.43
D-89075 Ulm
Germany

Physician: Dr. S. Albrecht, Dr. F. Schochter, Dr. A. Schramm, A. Polasik, T. Romashova, Prof. Dr. J. Huober, Prof. W. Janni
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Phone: +49 (0) 731 500 58520/-58521
Fax: +49 (0) 731 500 58526
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Complete information on the SAE may not be available initially. Initial SAE reports should be submitted as soon as the following minimum information has been obtained:

- EudraCT Number,
- patient identification number,
- the investigational medicinal product,
- an AE assessed as serious,
- name and address of investigator and clinical trial center.

In case of incomplete information at the time of initial SAE reporting, the initial report must be followed by further relevant information immediately after receipt. In certain cases it may be appropriate to follow-up the initial reports by several times.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

Please Note:

- An event which is part of the natural course of the disease under study (e.g. hospitalization for signs/symptoms of the disease or disease progression or death due to disease progression) does not need to be reported as a SAE even though serious criteria are met. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between protocol treatment or protocol design/procedures and the disease progression, then this must be reported as a SAE.
- For each serious adverse event a corresponding AE must be documented within the eCRF.

Every serious adverse event is followed up until it has subsided or stabilized.

11.3 Reporting of Pregnancies by the Investigator

If a patient has become pregnant, her study participation is terminated and the sponsor as well as the coordinating investigator is informed within 24 hours. Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported by the investigator using the same procedure as for SAE-reporting, specifying the date of conception, potential risks of pregnancy beyond intake of study medication and relevant obstetric history. He is to follow-up pregnancy complications and outcome. Congenital anomalies or birth defects are reported as Serious Adverse Events. In general follow-up for more than 8 weeks after due date is not required.

11.4 Sponsor Responsibilities

General Remarks:
When patient data are transferred as described below they must be pseudonymous. This means instead of data allowing patient identification the unique patient identification numbers are specified only.

AE Reporting:
On request of the competent authority detailed records have to be submitted on all adverse events which have been reported by the investigators

Annual Safety Report (ASR) with Serious Adverse Reaction (SAR) Listing:
All noxious and unintended responses to a medicinal product related to any dose are to be considered as adverse drug reaction (AR). "Response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Accordingly a Serious Adverse Reaction (SAR) is an AR which is serious according to the criteria given in section 11.2.

Once a year throughout the clinical trial as well as on request, the sponsor has to provide the competent authority and the competent ethics committee with a listing of all suspected serious adverse reactions (SARs) which have occurred over this period and with a report concerning the clinical trial participant's safety (annual safety report, ASR).

SUSAR and other Safety Issue Reporting:
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse reaction related to an investigational medicinal product (IMP) or comparators which occurs in the clinical trial, and which is both unexpected and serious. Adverse reactions are considered unexpected if not listed in the latest version of investigator's brochure (in case of lapatinib) or the "Fachinformation" (German SPC) (in case of drugs with marketing authorization).

Suspected unexpected serious adverse reactions (SUSAR) have to be reported to the competent authority and to the competent ethics committees immediately but within a maximum of fifteen days of first knowledge by the sponsor.

This also holds in case of any other issues which might require re-assessment of the risk-benefit ratio of the IMP. Such safety issues may be:

- single case reports of an expected serious adverse reactions with an unexpected outcome (e.g.: a fatal outcome),
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important,
- post-study SUSARs that occur after the patient has completed the clinical trial and are reported by the investigator to the sponsor,
- events relating to the conduct of the trial or the development of the investigational medicinal product likely to affect the safety of the subjects.

SUSARs which are fatal or life threatening must be reported within a time limit of 7 days. Relevant follow-up information must be provided within additional 8 days.

The sponsor also informs the investigators involved in the study immediately on any SUSARs which occur. The time limit also is 15 days. In case of fatal or life-threatening SUSARs the time limit is 7 days, further relevant information must be provided within additional 8 days.

Reporting of safety measures taken for patient protection:

Sponsor and investigator take immediate measures to protect trial participants from immediate hazard, if new or unforeseen conditions might compromise the participants' safety. In that case, the sponsor informs the competent authority and the ethics committee immediately about the measures taken and the conditions which caused their origination.

Reporting of clinical safety information to Novartis Pharma GmbH:
All serious adverse events occurring in a patient who has been treated with an IMP of Novartis Pharma GmbH shall be reported by the sponsor to Novartis Pharma GmbH within 24 hours after becoming aware of them.

All pregnancies occurring in a patient who has been treated with an IMP of Novartis Pharma GmbH shall be reported by the sponsor to Novartis Pharma GmbH within 2 week after becoming aware of them. All pregnancy complications (including early terminations of pregnancies) and their outcome shall be reported to Novartis Pharma GmbH. In general follow-up of pregnancies for more than 8 weeks after due date is not required. The status of mother and child at last follow-up examination shall also be reported to Novartis Pharma GmbH.

The sponsor will notify all SAEs and pregnancy reporting to Novartis Pharma GmbH (Abteilung Arzneimittelsicherheit; Roonstraße 25; 90429 Nürnberg; Fax-Nr.: 0911-27312985) on the appropriate report forms.

Reporting of safety information regarding denosumab to Amgen:
The sponsor will ensure that all AEs with a causal relationship to the concomitant medication denosumab will be captured within the study documentation. All pregnancies occurring in a patient who has been treated with denosumab shall be reported by the sponsor to Amgen within 1 working day after becoming aware of them.

All SADRs for denosumab will be forwarded to Amgen GmbH, Hanauer Strasse 1, 80992 München, Fax. 0800-2643651 on the appropriate forms within one working day after the sponsor became aware of them.

Reporting of safety information regarding lipegfilgrastim to TEVA:
The sponsor will ensure that all AEs with a causal relationship to the concomitant medication lipegfilgrastim will be captured within the study documentation.

All pregnancies occurring in a patient who has been treated with lipegfilgrastim shall be reported by the sponsor to TEVA within 1 working day after becoming aware of them.

All SADRs for lipegfilgrastim will be forwarded to TEVA GmbH, Graf-Arco-Str.3 89079 Ulm, on the appropriate forms within one working day after the sponsor became aware of them.

Oral adverse events reported as ONJ or as potentially representing ONJ will therefore be reviewed by the sponsor to determine whether criteria for ONJ are met. In addition all events of ONJ and potential ONJ will be sent to Amgen who will request the investigating site to provide all available source documents surrounding that event to be reviewed in line with processed for post marketing cases of (potential) ONJ by an independent adjudication committee.

12.0 TREATMENT DISCONTINUATION AND PREMATURE STUDY DISCONTINUATION

12.1 Protocol Treatment Discontinuation

12.1.1 *Criteria for Discontinuing Protocol Treatment*

Criteria for discontinuing standard chemo- or endocrine therapy:

- Tumor progression (as defined in section 10.2.1.)
- Toxicity (as defined in sections 8.2.3 and 8.2.4)
- Pregnancy
- Request by the patient
- For medical and any other reasons considered relevant by the physician

Criteria for discontinuing lapatinib treatment:

- Tumor progression (as defined in section 10.2.1.)
- Toxicity (as defined in sections 8.2.3 and 8.2.4)
- Pregnancy
- Request by the patient
- For medical and any other reasons considered relevant by the physician

12.1.2 *Duration of Protocol Treatment*

Duration of standard chemo- or endocrine therapy:

- depends on the agents and dose regimes chosen
- depends on the occurrence of tumor progression or other criteria for discontinuation (see section 12.1.1)
- does not exceed 12 months after randomization

  Note for clarification: For Patients of the control group whose protocol treatment (standard therapy without lapatinib) has a *planned* duration of *less than 12 months* the following applies:
  - In case the standard therapy regimen can be completed as scheduled (without need for premature discontinuation due to tumor progression or other criteria) these patients *remain in the "randomized treatment period"* after completion of standard therapy and the assessments of the "*control visits"* will be performed as described in section 9.1. This procedure will be continued until the patients present with tumor progression or – otherwise – until 12 months after randomization. In both cases the "conclusion visit of the randomized treatment period" will be performed and subsequently the "follow-up period" (as described in section 9.2.) will start.

Duration of lapatinib treatment:

- depends on the occurrence of tumor progression or other criteria for discontinuation (see section 12.1.1)
- the treatment with lapatinib can be extended if medically indicated. The drug will be supplied by Novartis Pharma GmbH on study terms for up to three years.

12.1.3 *Therapy after End of Protocol Treatment*

Therapy during the follow-up period for patients of the lapatinib group (standard chemo- or endocrine therapy with lapatinib):

- is at the discretion of the investigator, regardless of whether the protocol treatment could be administered for 12 months or had to be discontinued prematurely
- may include lapatinib for treatment of patients who may (further) benefit from lapatinib. 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).

Therapy during the follow-up period for patients of the control group (standard chemo- or endocrine therapy only):

- will be according to current guidelines and is at the discretion of the investigator, regardless of whether the protocol treatment could be completed as planned or had to be discontinued prematurely.

  Note for clarification: For Patients of the control group whose protocol treatment (standard therapy without

lapatinib) has a *planned* duration of *less than 12 months* the following applies:

- In case the standard therapy regimen can be completed as scheduled (without need for premature discontinuation due to tumor progression or other criteria) these patients *remain in the "randomized treatment period"* after completion of standard therapy and the assessments of the "*control visits"* will be performed as described in section 9.1. This procedure will be continued until the patients present with tumor progression or – otherwise – until 12 months after randomization. In both cases the "conclusion visit of the randomized treatment period" will be performed and subsequently the "follow-up period" (as described in section 9.2.) will start.

12.2 Premature Termination of Study Participation in Single Patients

Study participation is terminated prematurely with single patients

- on the patient's request,
- if in the investigator's opinion further participation would jeopardize the patient in an unjustifiable way.

If participation is terminated during the randomized treatment period every effort should be taken to perform the conclusion visit of the randomized treatment period (cf. section 9.1).

12.3 Discontinuation or Premature Termination of the Study in Single Sites

The sponsor, the coordinating investigator, the principal investigators, and the concerned competent authorities are reserved the right to initiate discontinuation or premature termination of the clinical trial in a single study site for the following reasons:

- Identification of a safety risk for the clinical trial participants of a single clinical trial center
- Non-compliance with the principles of GCP
- Insufficient recruitment
- Financial problems

If such action is considered, it is discussed with the principal investigator in advance.

If such action is taken the investigators and the principal investigator at the concerned trial center, the coordinating investigator and the sponsor must be informed immediately. It is the duty of the sponsor to notify the competent authority and the competent ethics committee within 15 days after premature termination or discontinuation. The principal investigator at the concerned center is to inform the local authority within the same time frame.

Furthermore, the clinical trial participants at the concerned trial center must be informed immediately about the discontinuation or termination. The investigator must ensure that the participants of the concerned study site are treated and followed-up appropriately. Date and time of the last application of the investigational drug as well as date and reason for the discontinuation or premature termination are to be documented in the participants' medical records and on the eCRFs.

In case of permanent discontinuation, all study materials (e.g. completed, partly completed and empty eCRFs) must be sent to the sponsor.

12.4 Premature Discontinuation of the Entire Study

The sponsor, coordinating investigator and the competent authorities may discontinue or terminate the entire study for the following reasons:

- Identification of a safety risk for the clinical trial participants
- Identification of problems with the trial design
- Non-compliance with the principals of GCP
- Insufficient recruitment of trial participants
- Financial problems

In consultation with the DSMB and the principle investigator the study should be discontinued by the sponsor, represented by Prof. Dr. W. Janni, due to safety concerns if any of the following reasons are present:

- If due to unexpected events the continuation of the study is not acceptable (ethical, medical or pharmaceutical legal aspects). This will be particularly the case,
  - if any grade 4 toxicity occurs in > 20 % of the patients
  - if febrile neutropenia (defined as grade 3 or 4 neutropenia + fever > 38.5 C°) occurs in > 20 % of the patients
  - if grade 4 neutropenia occurs in > 20 % of the patients
  - if an unexpected amount of SUSARs occurs
  - if hand-foot-syndrome grade 4 occurs in > 30 % of the patients

In the event of study termination, steps will be taken to ensure subjects transition smoothly off study, and if the risk/benefit profile is deemed to be appropriate, subject may continue to receive study treatments at the discretion of the investigator.

All investigators and the sponsor must immediately be informed about the discontinuation or premature termination. The principal investigator at each study site must notify the local competent authority within 15 days after premature termination. The sponsor is to notify the competent authority and the competent ethics committee within the same time interval.

Furthermore, all clinical trial participants must be informed immediately about discontinuation or premature termination. The responsible investigators must ensure that the clinical trial participants are treated and followed up appropriately. Date and time of the last application of the investigational medicinal product as well as date and reason for the discontinuation or premature termination are to be documented in the participants' medical records and on the eCRFs.

In case of permanent discontinuation, all study materials must be sent to the sponsor.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 CTC Counts and Assessment of HER2 Status on CTCs

CTC counts and assessments on HER2 status are carried out by the laboratories named on page 3 of this protocol. For further information refer to section 2.2.

13.2 Tumor Tissue Sampling

If a biopsy of a metastatic site is carried out as part of the routine diagnostic work-up or a tumor block of the primary tumor is available, a sample of tumorous tissue will be investigated for further translational research.

14.0 STATISTICAL CONSIDERATIONS

14.1 Statistical Objectives

The primary objective of this study is to prove the clinical efficacy of lapatinib in patients with metastasizing breast cancer who exhibit HER2-positive circulating tumor cells (CTC) although examination of primary tumor tissue and/or biopsies from metastatic sites found HER2-negativity. Confirmatory analysis is performed by comparison of the *CTC clearance rate* in patients receiving standard anticancer therapy with lapatinib and patients receiving a standard anticancer therapy but no HER2 inhibitor.

The secondary objective of the trial is to assess the level of compliance to study procedures.

14.1.1 *Primary Variable*

The primary target value of this study is the comparison of the CTC clearance rate between the two study arms. CTC clearance rate is defined as the 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 CellSearch® System; Veridex LLC, Raritan, USA)

14.1.2 *Secondary Variables*

Secondary target variables related to efficacy comprise variables based on tumor response and survival. The following secondary variables are of interest:

- *Progression free survival (PFS)* of a patient being defined as the time in months from date of randomisation (i.e. start of the first therapy cycle) until progressive disease (PD) or death from any cause, whichever comes first
- *Response rates (overall response rate, clinical benefit rate),* i.e. percentage of patients showing overall response (CR+PR); percentage of patients showing CR, PR or SD
- *Overall survival (OS)* of a patient being defined as the time in months from date of randomisation (i.e. start of the first therapy cycle) to death
- *Dynamic of CTC*
- *Safety and tolerability*
- Assessment of *Quality of life* over time as defined by EORTC QLQ-C30 and EORTC QLQ-BR23
- Level of compliance to study protocol
- *Intensity of pain* as measured by numeric rating scale (NRS)
- Incidence and type of AE in terms of:
  - All AE,
  - Related AE,
  - SAE,
  - Related SAE,
  - NCI-CTC (version 4.03) grade 3 and 4 AE,
  - Related NCI-CTC (version 4.03) grade 3 and 4 AE,
  - AE leading to treatment discontinuation,
  - Incidence of, and reason for, deaths.

14.2 Study Populations

The following study populations will be examined:

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.

14.3 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.

14.4 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.

14.5 Safety Analysis

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. Steps will be taken to preserve data confidentiality and to ensure the scientific integrity of the ongoing study. The safety analysis will be conducted on all patients who received at least one dose of the study treatment. Recruitment will not be suspended while this safety analysis is undertaken, except if the stopping thresholds specified below (cf. Premature Discontinuation) are exceeded or on recommendation of the safety review committee (DSMB) for extenuating circumstances (e.g. delay in data retrieval or analysis, emerging unforeseen safety concerns). Every effort will be made to minimize the time from the analysis cut-off date to data retrieval, analysis, and safety review decision. In case of unexpected toxicity the advisory board and the DSMB will be informed and give their advisory vote. Based on the recommendations of this team, a protocol amendment may be implemented to modify dose or study procedures. The safety review is not limited to these adverse events for which stopping rules are established; in the event that other safety concerns are identified, the study could also be closed. All SAEs which are reported to the Sponsor as required by the protocol will be reviewed during this safety analysis. In addition to this safety analysis of the first cohort, ongoing individual events will be reviewed on an ongoing basis, according to routine protocol and pharmacovigilance procedures. Furthermore, the safety data will be monitored at least once a year.

15.0 PUBLICATION POLICY

The results of this study will be published. The responsibility is with the coordinating investigator.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Issues

This study is conducted in compliance with the Declaration of Helsinki (1996), the GCP-Guidelines of the International Conference on Harmonization and applicable German drug law.

16.2 Institution Eligibility for Participation

The sponsor acquires information on the potential study site including:

- the potential principal investigator's interest in study participation
- his general experience in the conduct of clinical trials and his experience in similar studies (number of trials performed, number of patients attended in clinical trials)
- previous audits and inspections
- suitability of the site facility for study purposes with special regard to radiology
- emergency equipment, accessibility of the emergency unit of a hospital

16.3 Favorable Opinion of the Competent Ethics Committee and Official Study Approval

On behalf of the sponsor the coordinating investigator will care, that a favorable opinion of the competent ethics committee on study conduct and approval of the study by the competent authority is obtained. No patient must be included before both have been granted.

Contact data:
Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
Probandenkontakttelefon: Frau Kovac
Kurt-Georg-Kiesinger-Allee 3
53175 Bonn
Tel.: 0228-207-4318 //
Stichwort „Fachgebiet Klinische Prüfung / Inspektionen"

16.4 Informed Consent

Patients are only requested to participate in the study, if they suffer from metastasizing breast cancer, if their primary tumor and/or a biopsy from a metastatic site was examined and found to be HER2-negative, and if there is the indication to initiate a standard chemo- or endocrine therapy allowed in this study. Since such patients are expected to be under extreme emotional stress they are intended not to be unduly bothered with detailed information on the study before HER2 status on CTC is known. Therefore informed consent is obtained in two steps. At first patients are asked to consent in blood sampling for CTC count and assessment of HER2 status on CTC (patient information and consent form – part 1). If HER2 status on CTC is positive, their informed consent in study participation is requested (patient information and consent form – part 2). In addition, when both consents have been obtained, patients are also requested to consent in blood sampling for translational medical investigations (patient information and consent form – part 3).

Before signing a consent form, patients are informed about the study orally and in writing. Oral information is to be given by an investigator and must include the information given in the respective information leaflets used for written information (patient information – parts 1 to 3). Patients are given ample opportunity to enquire details of the trial and discuss all questions they have. They are left sufficient time to decide on whether to give their consent or not.

The consent forms must be personally signed and dated by the patient and by the investigator who conducted the informed consent discussion. The signed consent forms are retained as part of the trial files. A copy of the consent forms and copy of the information leaflets used are left to the patient.

Before the first informed consent has been obtained no study specific procedure may be carried out. Thereafter only blood sampling for CTC count and assessment of HER2 status is allowed. Further study specific procedures may only be carried out after the second informed consent has been given. Blood samplings for translational medical investigations will only take place if informed consent to these additional examinations is obtained (part 3). If a patient objects, no blood sample will be taken for this purpose, but may nevertheless participate in the study.

The written informed consent forms and any other written information to be provided to patients are revised whenever important new information becomes available that may be relevant to the patient's consent. The sponsor obtains the competent ethics committee's favorable opinion on any revised written informed consent form or and written information material in advance of use. The investigator informs patients already included in a timely manner if new information becomes available that may be relevant to their willingness to continue participation. The communication of this information is documented.

16.5 Data Protection

All national and local legal requirements regarding data protection will be adhered to. All study findings and documents will be regarded as confidential. The investigator and other authorized persons will not disclose such information without prior written approval from the sponsor.

Pseudonymity of patient data is assured by means of a patient identification number that will be allocated via eCRF. Each patient will be clearly identified through the patient number and randomization number given in the enrolment procedure. At the center site the investigator compiles a confidential list, in which the patient name and address is assigned to the patient number.

Throughout documentation, evaluation and notification procedures, the participants will be identified on eCRFs and other documents by their unique participant identification number. If the name, the initials or the year of birth of a participant appear on a document (e.g. laboratory report), that has to be transferred within the notification duties (e.g. to the sponsor or to competent authorities), these data will be obliterated before a copy of the document is transferred. Documents which identify the trial participants (e.g. patient identification log and the signed informed consent forms) will be maintained in confidence by the principal investigator. The participants will be told that all study data will be stored on computer and handled in strictest confidence.

The trial participants are informed that monitors, representatives of the sponsor, the ethics committee and the concerned competent authorities including the local competent authority may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with legal data protection requirements. Patients' agreement to this is part of the informed consent forms parts 1-3.

16.6 Data Management

16.6.1 *Collection of Data*

Study data are captured by means of the eCRF. Data are only entered by members of the site personal who

- have been assigned this competency in the site delegation log (a document to be kept in the ISF, defining the responsibilities of each member of the site personal),
- have participated in a required training on handling the eCRF,
- have been provided password protected access to the eCRF.

The personal password a member of the site personal has been provided must not be disclosed to any other person whether involved in the study or not.

Data is to be entered in a timely manner.

16.6.2 *Data Management*

The data management for this study will be performed by Alcedis GmbH, Winchesterstr. 3, D-35394 Gießen.
The following sections describe the software employed and measures applied for data security.
Data are recorded, processed and stored using the following software tools:

a) eCRF database (Location: Alcedis)
b) SAE database (Location: Alcedis)

Wherever applicable, current GCP guidelines, actual technical standards and guidelines are observed.

Employed Software

eCRF database:

For data capturing and data management of this clinical trial, a web-based validated software (WBDC) based on a relational database will be employed. The software consists of the following modules:

a) Administration:	Administration of sites (clinics/office based physicians) by system administrator and project management. Within the individual sites the following system users are defined: Investigator and study nurse. All access rights are administered in a role-based security system.
b) Forms / Form validator:	Electronic Case Report Forms (eCRFs) for data capture including online validation of eCRFs during data capture, e.g. check on range, plausibility, type mismatch. In addition to the system based plausibility checks, a formal query process will be implemented to resolve inconsistencies in data.
c) Reports:	Dynamic report generator, e.g. reports for investigators on CRF status.
d) Query management:	After completion of data entry checks for plausibility, consistency and completeness of the data will be performed. Based on these checks, queries will be produced combined with the queries generated by manual checks. All missing data or inconsistencies will be reported back to the center(s) through the eCRFs and clarified by the responsible investigator. If no further corrections are to be made in the database it will be declared closed. With the export engine of Alcedis MED, data sets for the statistical analysis were generated.

The employed technology and technical requirements for data entry on site are as follows:

a) The used software is completely server-based, i.e. all programme processes are executed centrally on a web or database server.
b) Data are saved exclusively in the central database server. This server is located in the facilities of Alcedis GmbH, Winchesterstr. 3, D-35394 Gießen.
c) For system access, users require a conventional desktop computer with internet access.

16.6.3 *Data Security and Storage*

For client / server communication via the internet only encrypted transmissions are applied. State of the art encryption technology is used exclusively. For data transmission in this clinical trial an encryption level (128-bit) is employed by means of the Secure Socket Layer Algorithm (SSL).
In addition, the server identifies itself to the client workstation by means of a digital server certificate issued by an authorised certification authority. This ensures that data are sent only to the server of Alcedis GmbH.

Data are protected from potential virtual attacks and physical damage.
Views on data or reports as well as edit or read only rights are controlled with individual passwords. Access authorisation to the eCRF databases is granted individually to investigators and programme personnel by means of user accounts.
The project management of the CRO has a read-only access on all patient data stored in the eCRF database.

Assurance of data will be made by RAID-Systems (Redundant Array of Independent Disks), thereby ensuring data security even if one hard disc failed.

Furthermore a back up onto magnetic tape is performed according to the following scheme:

- daily back-up over a period of 7 days
- weekly back-up over a period of 5 weeks
- monthly back-up over a period of continuance of the clinical trial

Investigators will get a CD-Rom after the end of the trial containing the data of the patients they have documented.

16.6.4 *Data Processing*

The study personnel must care that any data transferred outside the trial center do not allow identification of the patient. Data on clinical trial participants which are to be transferred to the sponsor, the data management, the

competent ethics committee, the competent authority or investigators from other sites must identify the patient only by means of the unique patient identification number.

Data management checks the data entered in the eCRF for completeness and plausibility. In case of findings queries are issued for clarification.

16.6.5 *Archiving*

Essential study documents are archived for at least 10 years after completion of the trial. The trial master file (TMF) is kept by the sponsor. The ISF is to be archived at the respective site.

The source documents which are created in the clinical trial center are to be filed in the participant's medical records. They are archived at the site in accordance with local requirements.

16.7 Quality Assurance

16.7.1 *Responsibilities*

The sponsor assumes the responsibility that this clinical trial is planned and conducted in accordance with the quality requirements of the principles of GCP.

16.7.2 *Monitoring*

Study monitoring is undertaken by monitors appointed by Alcedis GmbH, Winchesterstr. 3, D-35394 Gießen.

The responsible monitor will be allowed, on request, to inspect the various records of the trial (Case Report Forms, patient file and other pertinent data).

Due to the electronic documentation system checks for range and plausibility are performed during data entry. The monitor gets an access to read the data only.

In line with ICH GCP guidelines, monitoring will include verification of data entered in the eCRF against original patient records. This verification will be performed by direct access to the original subject records, and the sponsor guarantees that patient confidentiality will be respected at all times. Participation in this study will be taken as agreement to permit direct source data verification.

16.7.3 *Audits and Inspections*

Independent of and separate from routine monitoring the sponsor and authorities may perform audits and inspections respectively. The investigator must allow specially trained representatives of the sponsor and of the authorities to accede the site and to inspect all relevant facilities and documents.

16.7.4 *Notification of the Local Authority*

The CRO will notify the local authority as required by §67 AMG in conjunction with § 12 GCP-V. The principal investigator of each site will inform the CRO about any change in study personnel, so that the notifications can be done timely.

16.7.5 *Definition of Source Documents*

The hospital patient records are the only source documents. No data are entered directly into the eCRF.

16.8 Insurance Cover

As required by the principles of GCP and §40(1) of the German Drug Law the sponsor takes out an insurance policy for all clinical trial participants via the annual contract of the University Hospital Ulm.

Insurance provider:
HDI-Gerling Versicherung AG
Police-No.: 56 206450 03016

Anmeldenummer: 0903 2010 108

Contact data:
HDI-Gerling Industrie Versicherung AG
Riethorst 2; 30659 Hannover
Tel. 0511-645-0
Fax 0511-645-4545
Web: www.hdi-gerling.de

The insurance policy covers all injuries patients suffer due to study participation. Compensation is limited to 500 000 Euro at most.

The investigator informs each patient on his responsibilities resulting from the terms of insurance. Patients participating in the study must neither undergo any other medical treatment during the clinical trial without prior information of the investigator (except for cases of emergency) nor participate in any other trial. In case of damnification which might be due to trial participation, a patient must inform investigator and insurance immediately and cooperate in the clarification of whether there is a causal relationship between damnification and study participation.

16.9 Financing

This clinical trial is supported by Novartis Pharma GmbH. The company also provides the study medication free of charge. This clinical trial is supported by Pierre Fabre Pharma GmbH, 79111 Freiburg. The company also provides Navelbine free of charge. The company TEVA GmbH, 89079 Ulm provides Myocet® free of charge and gives financial support. This clinical trial is supported by AMGEN GmbH, 80700 Munich.

This research is conducted with support from the Investigator-Initiated Study Program of Veridex, LLC.

16.10 Honorarium for Clinical Trial Participants

Patients are not remunerated for study participation.

16.11 Patient ID Card

Patients are provided an ID card as specified in APPENDIX X – PATIENT ID CARD.

This card also includes all information required according to § 5(8) GCP-V (German directive on GCP), that is not specified on the labels of lapatinib bottles.

16.12 Data Safety Monitoring Board (DSMB)

A DSMB will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. Exact operating procedures are set up before the start of the study.

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17.2 CLINICAL TRIALS

NCT00148902 (ClinicalTrials.gov Identifier); Other Study ID Numbers: EGF10021; A Phase I, Open-Label Study of the Safety, Tolerability and Pharmacokinetics of GW572016 in Combination With Docetaxel (TAXOTERE); Sponsor: GlaxoSmithKline; Study Director: GSK Clinical Trials, MD; Results summary: http://www.gsk-clinicalstudyregister.com/index.jsp (last access: 25.03.2011)

NCT00251433 (ClinicalTrials.gov Identifier); Other Study ID Numbers: EGF100161; An Open-label, Multicenter, Phase I/II Dose Escalation Study of Oral GW572016 in Combination With Docetaxel (Taxotere) Plus Trastuzumab (Herceptin) in Subjects Previously Untreated for ErbB2-overexpressing Metastatic Breast Cancer; Sponsor: GlaxoSmithKline; Study Director: GSK Clinical Trials; Results summary: http://www.gsk-clinicalstudyregister.com/index.jsp (last access: 25.03.2011)

NCT00356811 (ClinicalTrials.gov Identifier); Other Study ID Numbers: EGF105764: An Open-Label, Single-Arm, Multi-Centre, Phase II Study of Oral Lapatinib in Combination With Paclitaxel as First-Line Treatment for ErbB2-Am Study Director: GSK Clinical Trials plified Metastatic Breast Cancer Patients; Sponsor: GlaxoSmithKline; Study Director: GSK Clinical Trials; Results summary: http://www.gsk-clinicalstudyregister.com/index.jsp (last access: 25.03.2011)

NCT00709618 (ClinicalTrials.gov identifier); Other Study ID Numbers: LPT111110: A Phase II, Single-Arm, Multi-Center Study Evaluating the Combination of Vinorelbine and Lapatinib in Women With ErbB2 Overexpressing Metastatic Breast Cancer; Sponsor: GlaxoSmithKline; Study Director: GSK Clinical Trials. (last access: 25.03.2011)

NCT01013740 (ClinicalTrials.gov identifier); Other Study ID Numbers: 112620; VITAL-Study; A Phase II, Randomised, Multi-Centre Study Evaluating Lapatinib in Combination With Vinorelbine or Capecitabine in Women With ErbB2 Overexpressing Metastatic Breast Cancer; Sponsor: GlaxoSmithKline; Study Director: GSK Clinical Trials (last access: 25.03.2011)

NCT01044485 (ClinicalTrials.gov identifier); Other Study ID Numbers: 0205-1isni 07 / 001.112:A Multicenter Open-label, Phase I/II Dose Escalation Study of Oral Lapatinib in Combination With Docetaxel in Patients With HER-2 Positive Advanced or Metastatic Breast Cancer; Sponsor: Centre Georges Francois Leclerc; Principal Investigator: Nicolas Isambert, M (last access: 25.03.2011)

NCT01172223 (ClinicalTrials.gov identifier); Other Study ID Numbers: LAPADO-Study, 2007-000924-42, Phase I/II Trial of Primary Chemotherapy With Non-pegylated Liposomal Doxorubicin, Paclitaxel and Lapatinib in Patients With HER2-positive

Early; Sponsor: Sana-Klinikum Lichtenberg; Principal Investigator: Dirk Elling Sana Klinikum Lichtenberg, Berlin (last access: 30.03.2011)

EUDRACT-NR.: 2010-024238-46	**Protokoll-Nr.:** D-III

Sponsor: Universitätsklinikum Ulm, Albert-Einstein-Allee 29, D-89081 Ulm
Wissenschaftliche Leitung: Prof. Dr. Wolfgang Janni, Universitätsklinik Ulm

Leiterin der klinischen Prüfung:
Prof. Dr. Tanja Fehm, Heinrich-Heine-Universität Düsseldorf, Moorenstraße 5, 40225 Düsseldorf

Titel: DETECT III – Multizentrische, prospektiv randomisierte Phase III Studie zum Vergleich einer antineoplastischen Therapie allein versus einer antineoplastischen Therapie plus Lapatinib bei Patientinnen mit initial HER2-negativem metastasiertem Brustkrebs und HER2-positiven zirkulierenden Tumorzellen.

Studienmedikation: Lapatinib (Tabletten 250 mg)

Behandlung und Dosierung
Studientherapie:
Die Chemo- oder endokrine Therapie nach Standard erfolgt gemäß den Empfehlungen der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO). Die individuelle Therapienentscheidung erfolgt nach Ermessen des verantwortlichen Prüfarztes unabhängig von der klinischen Studie.

Therapie mit Lapatinib:
Die Therapie mit Lapatinib wird den entsprechend randomisierten Patientinnen zusammen mit der indizierten Chemo- oder endokrinen Therapie verabreicht. Die Lapatinib-Einnahme erfolgt einmal täglich möglichst zur gleichen Tageszeit mindestens eine Stunde vor oder mindestens eine Stunde nach einer Mahlzeit. Die Behandlung mit Lapatinib sollte - wenn medizinisch indiziert – über die randomisierte Phase hinaus verlängert werden. Die Lapatinib-Dosierung erfolgt in Abhängigkeit von der vorgesehenen Chemo- oder endokrinen Therapie. Es dürfen nur mit Lapatinib zugelassene Medikamentenkombinationen verwendet werden, oder Medikamentenkombinationen mit Lapatinib, die bereits der klinischen Prüfung unterliegen. Die empfohlenen Behandlungspläne sind in der folgenden Tabelle aufgeführt:

Lapatinib + Monochemotherapie	**Empfohlener Behandlungsplan**
Lapatinib + Docetaxel	Lapatinib 1250 mg p.o./die + Docetaxel 75 mg/m² d1 q3w, dann Lapatinib mono 1500 mg /die. Die Dauer der Behandlung mit Docetaxel erfolgt nach Ermessen des Prüfarztes. Primärprophylaxe mit Lipegfilgrastim (Lonquex®): Gabe von 6 mg 24 h nach der Verabreichung von Docetaxel, sofern keine Kontraindikationen bestehen.
Lapatinib + Paclitaxel	Lapatinib 1500 mg p.o./die + Paclitaxel 80 mg/m²/weekly, oder Lapatinib 1500 mg p.o./die + Paclitaxel 175 mg/m² d1, q3w, dann Lapatinib mono 1500 mg/die. Die Dauer der Behandlung mit Paclitaxel erfolgt nach Ermessen des Prüfarztes.
Lapatinib + Capecitabin	Lapatinib 1250 mg p.o./die + Capecitabin 2000 mg/m² d1-14, q3w, dann Lapatinib mono 1500 mg/die. Die Dauer der Behandlung mit Capecitabin erfolgt nach Ermessen des Prüfarztes.
Lapatinib + Vinorelbin	Lapatinib 1000 mg p.o./die + Vinorelbin p.o.* 50 mg/m² d1, 8 q3w, dann Lapatinib mono 1500 mg/die. Die Dauer der Behandlung mit Vinorelbin erfolgt nach Ermessen des Prüfarztes.
Lapatinib + NPLD (non pegylated liposomal Doxorubicin)	Lapatinib 1250 mg p.o./die + NPLD 60 mg/m² d1 q3w, dann Lapatinib mono 1500 mg/die. Die Dauer der Behandlung mit NPLD erfolgt nach Ermessen des Prüfarztes.
Lapatinib + endokrine Monotherapie	**leitliniengerechtes Therapieschema**
Lapatinib + Aromatase-Inhibitoren (AI)	Lapatinib 1500 mg p.o./die + AI als Monotherapie nach Fachinformation

*Im Fall von Gegenanzeigen für orales Vinorelbin, kann i.v. Vinorelbin 20 mg/m² d1, 8 q3w in Kombination mit

Lapatinib 1250 mg p.o./die als Alternative eingesetzt werden.

Nach Beginn der Behandlung mit Lapatinib wird die Lapatinib-Dosierung je nach Dosierung der verabreichten Standard-Therapie und in Abhängigkeit der aufgetretenen Nebenwirkungen angepasst. Die tägliche Maximaldosis von Lapatinib beträgt 1500 mg, die tägliche Minimaldosis 750 mg. Die Gabe von Lapatinib erfolgt über 12 Monate und kann nach der Behandlungsphase bei entsprechender medizinischer Indikation verlängert werden. Lapatinib wird unter Studienbedingungen von Novartis Pharma GmbH für die Dauer der individuellen Studienteilnahme (inklusive 2 Jahre Follow-Up-Phase) zur Verfügung gestellt. Ein vorzeitiger Abbruch der Therapie erfolgt bei Progress der Erkrankung oder aus anderen Gründen für einen vorzeitigen Therapieabbruch. Die Dauer der Gabe der Standard- Chemo- oder endokrinen Therapie erfolgt leitliniengerecht und ist abhängig von der gewählten Dosierung sowie dem Auftreten eines Progresses der Erkrankung. Eine Beendigung oder Modifikation der Standard-Chemo- oder endokrinen Therapie ist entsprechend der Einschätzung des behandelnden Arztes auch aus anderen Gründen möglich.

Standard Chemo- oder endorkine Therapie (während der randomisierten Behandlungsphase)
Die Chemo- oder antihormonelle Therapie im Monotherapie-Arm soll gleich dosiert werden wie in der Kombinationstherapie mit Lapatinib.

Monochemotherapie	**Empfohlene Dosierung**
Docetaxel	75 mg/m² i.v. d1 q3w
Paclitaxel	80 mg/m² i.v. weekly oder 175 mg/m² d1 q3w
Capecitabine	2 x 1000 mg/m² p.o. d1-14 q3w
Vinorelbine	50 mg/m² p.o.* d1+d8 q3w (Dosiseskalation nach Verträglichkeit möglich)
NPLD	60 mg/m² i.v. d1 q3w
Endokrine Monotherapie	**Empfohlene Dosierung**
Exemestan	25 mg/d p.o.
Letrozol	2,5 mg/d p.o.
Anastrozol	1 mg/d p.o.

Tabelle 2: Behandlungsmöglichkeiten der Monochemo- oder endokrinen Therapie
*Bei Kontraindikation einer oralen Behandlung mit Vinorelbine, kann Vinorelbine intravenös 20 mg/m² d1, 8 q3w verabreicht werden (Dosiserhöhung nach Verträglichkeit möglich).

Therapie von ossären Metastasen mit Denosumab:
Alle Patientinnen mit ossären Metastasen sollen mit Denosumab (Xgeva® 120 mg, s.c. q4w) therapiert werden. Patientinnen, die vor Studienbeginn mit Bisphosphonaten behandelt wurden, werden – sofern keine Kontraindikationen vorliegen (wie z.B. eine ausgeprägte, unbehandelte Hypocalcämie oder Hypersensitivität gegenüber Denosumab oder den Arzneistoffträgern) - auf Denosumab umgestellt

Behandlung in der Follow-Up-Phase:
Die Therapie in der Follow-Up-Phase, d.h. nach Abschluss der Studientherapie erfolgt gemäß den Empfehlungen des Prüfarztes.

Indikation
Metastasierter Brustkrebs mit der Indikation zur antineoplastischen Standardtherapie und HER2-positiven zirkulierenden Tumorzellen (CTC) bei HER2-negativem Primärtumor und HER2-negativen Gewebeproben einer metastatischen Läsion.

Rationale der Studie
Evaluation der Wirksamkeit von Lapatinib bei Patientinnen mit metastasiertem Brustkrebs, welche HER2-positive zirkulierende Tumorzellen (CTC) aufweisen, obwohl der Primärtumor und/oder Gewebeproben einer metastatischen Läsion auf ihren HER2-Status getestet wurden und HER2-Negativität zeigten.
Evaluation der Patientencompliance zum Studienablauf.

Primäres Zielkriterium:
- *CTC Clearance Rate: Anteil an Patientinnen mit mindestens einer vor Behandlungsbeginn in 7.5 ml peripherem Blut nachgewiesenen zirkulierenden Tumorzelle (CTC), bei denen nach der Behandlung keine CTCs im Blut mehr nachgewiesen werden können (CTC Nachweis erfolgt mit dem CellSearch® System; Veridex LLC, Raritan, USA)*

Sekundäre Zielkriterien:

- *Progressionsfreies Überleben (PFS)*
- *Allgemeine Ansprechrate: Komplettremission (CR), Teilremission (PR)*
- *Klinische Erfolgsrate*
- *Gesamtüberleben*
- *Dynamik der zirkulierenden Tumorzellen*
- *Evaluation der Lebensqualität (EORTC QLQ-C30 und EORTC QLQ-BR23 Fragebögen)*
- *Toxizitätsanalyse von Lapatinib: Sicherheit und Verträglichkeit*
- *Compliance*
- *Schmerzanalyse: Messung anhand einer Numerischen Rating-Skala (NRS)*

Studiendesign

Multizentrische, prospektiv randomisierte, zweiarmige Phase III Studie

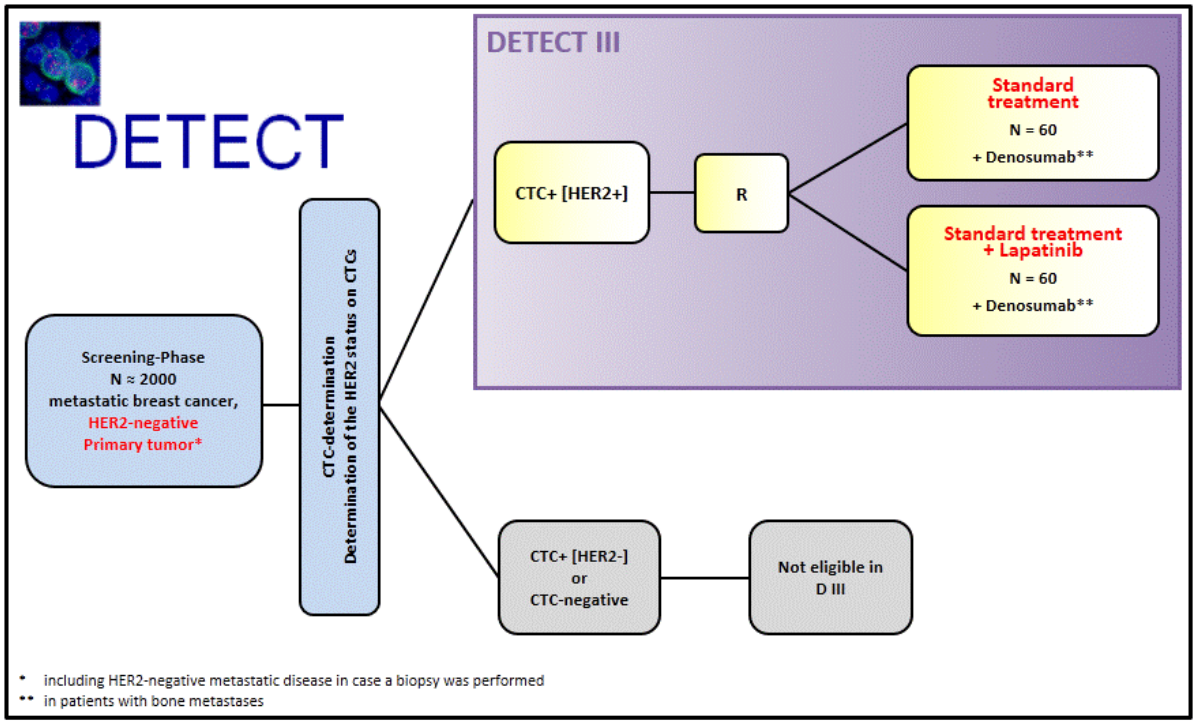


Abbildung: Klinisches Studiendesign

Gesamtstudiendauer:

Rekrutierungsdauer: 95 Monate

Maximale Studiendauer: 131 Monate und 3 Wochen (Januar 2012 bis Januar 2023)

Individuelle Studiendauer:

Die individuelle Studienbeteiligung beginnt mit dem Screening-Besuch und endet mit dem Tod der Patientin.

- maximale Dauer der Vorbehandlungsphase/Evaluierungsphase (von Screening bis Randomisierung): 3 Wochen
- maximale Dauer der Behandlungsphase im Rahmen der Studienteilnahme: 12 Monate
- geschätzte Maximaldauer der Follow-Up-Phase: 24 Monate

Die geschätzte Maximaldauer der individuellen Studienteilnahme beträgt 36 Monate und 3 Wochen.

Prüfzentren: Bis zu 100 Prüfzentren deutschlandweit

Einschlusskriterien

1. Schriftliche Einverständnis zur Studienteilnahme
2. Metastasiertes Mammakarzinom, das einer Operation oder der Strahlentherapie allein nicht zugänglich ist. Histopathologische Sicherung des primären Mammakarzinoms oder einer metastatischen Läsion des Mammakarzinoms und Bestimmung des Östrogen- und Progesteronrezeptorstatus
3. Bestimmung des HER2-Status des primären Mammakarzinoms und/oder einer metastatischen Läsion. HER2-Negativität aller untersuchten Gewebeproben, d.h. Immunhistochemie 0-1+ oder 2+ und Fluoreszenz in situ Hybridisierung (FISH) negativ oder nur FISH negativ.

Bei Patientinnen, bei denen keine standardmäßige HER2-Testung zum Zeitpunkt der Primärdiagnose verfügbar war und keine Biopsie einer metastatischen Läsion vorliegt, wird von einem HER2-negativen Primärtumor ausgegangen.

4. Nachweis HER2-positiver zirkulierender Tumorzellen (CTC) (HER2-Status ermittelt über IHC oder FISH)
   - Mindestens eine CTC/7.5 ml Blut (CellSearch® Circulating Tumor Cell Kit) und
   - Mindestens eine HER2-positive CTC
5. Indikation zur Standard-Chemo- oder endokrinen Therapie, deren Kombination mit Lapatinib zugelassen ist (Tyverb® 250 mg Tabletten) oder in klinischen Studien evaluiert wird
6. Tumorevaluation innerhalb von 6 Wochen vor Studienrandomisierung
7. Mindestens eine nach RECIST auswertbare metastatische Läsion, entsprechend den RECIST Leitlinien Version 1.1. Patienten mit messbaren und nicht-messbaren Läsionen können eingeschlossen werden. [Eisenhauer 2009]
8. Alter ≥ 18 Jahre
9. ECOG ≤ 2
10. Adäquate Knochenmarksreserve und Organfunktion
    - Absolute Neutrophile ≥ 1500/µL,
    - Thrombozyten ≥ 100000/µL,
    - Hämoglobin ≥ 9g/dL,
    - ALT (SGPT) ≤ 3.0 × ULN,
    - AST (SGOT) ≤ 3.0 × ULN,
    - Bilirubin (gesamt) ≤ 2 × ULN und ≤ 35% direkt
    - Kreatinin ≤ 2.0 mg/dl oder 177µmol/L

Cave: Die oben genannten Angaben gelten nur für eine Therapie mit Lapatinib. Zur Verabreichung der Standard-Chemo- oder endokrinen Therapie muss die aktuelle Fachinformation zusätzlich berücksichtigt werden.

11. Echokardiographischer Nachweis einer ausreichenden linksventrikulären Ejektionsfraktion innerhalb des Referenzbereichs der jeweiligen Institution
12. Bei gebärfähigen Patientinnen gilt:
    - Negativer Schwangerschaftstest (minimale Sensitivität 25 IU/L oder äquivalente Einheiten des HCG) innerhalb von 7 Tagen vor Randomisierung
    - Sichere Kontrazeption (d.h. nicht-hormonelle Kontrazeption, IUP, Anwendung einer Doppelbarriere-Methode, Vasektomie des Geschlechtspartners, komplette sexuelle Abstinenz) andauernd über mindestens 28 Tage nach Komplettierung der Studientherapie.

Ausschlusskriterien

1. Anamnestisch bekannte Überempfindlichkeit gegenüber Lapatinib oder chemisch verwandten Substanzen
2. Mehr als 3 palliative Chemotherapie-Linien (dabei ist eine Chemotherapie-Linie definiert als jede neue Chemotherapie und jede Modifikation eines bestehenden Chemotherapieregimes)
3. Behandlung mit Prüfsubstanzen oder andere antineoplastische Therapie während der Studie oder innerhalb von 2 Wochen vor Randomisierung oder 6 Wochen im Fall von Nitrosourea oder Mitomycin C
4. Persistierende, therapeutisch relevante Nebenwirkungen einer vorangegangenen antineoplastischen Therapie während des Randomisierungszeitraums > Grad 1 (NCI CTCAE)
5. Anti-retrovirale Therapie aufgrund einer HIV-Infektion
6. Aktuelle Leber- oder Gallenwegserkrankung (mit Ausnahme von Patientinnen mit Gilberts-Syndrom, mit asymptomatischen Gallensteinen, Lebermetastasen oder stabiler chronischer Lebererkrankung)
7. Vorliegen einer Erkrankung, die die adäquate Einschätzung oder Evaluation der Studiendaten stören könnte, oder Vorliegen einer anderen medizinischen Indikation, bei der die Patientin durch eine Studienteilnahme unverhältnismäßig gefährdet ist
8. Zweitkarzinom innerhalb der letzten 3 Jahre (außer in-situ-Karzinom der Cervix uteri oder Basaliom der Haut)
9. Unfähigkeit der oralen Aufnahme der Studienmedikation (z.B. bei Malabsorptionssyndrom, parenteraler Ernährung, vorangegangenen chirurgischen Eingriffen, die die Absorption beeinflussen (z.B. Dünndarm- oder Magenresektionen), oder bei unzureichend therapierten entzündlichen Darmerkrankungen (z.B. M. Crohn, Colitis ulcerosa))
10. Manifeste kardiale Vorerkrankung, definiert als:
    - instabile Angina pectoris in der Vorgeschichte,
    - therapiebedürftige oder klinisch relevante Arrhythmien in der Vorgeschichte (ausgenommen asymptomatisches Vorhofflimmern, welches einer Antikoagulation bedarf),
    - Z. n. Myokardinfarkt innerhalb der letzten 6 Monate vor Studieneintritt,
    - symptomatische Herzinsuffizienz,

- Ejektionsfraktion < 50% oder unterhalb des oberen Referenzbereichs der jeweiligen Institution
- jede andere kardiale Begleiterkrankung, die nach Ansicht des behandelnden Arztes zu einer unverhältnismäßigen Gefährdung der Patientin bei Studienteilnahme führen würde

11. Demenz, veränderter mentaler Status oder andere psychiatrische oder soziale Einflüsse, die das Verständnis oder die Wiedergabe der informierten Einwilligung verhindern oder welche die Einhaltung des Studienprotokolls stören
12. Lebenserwartung < 3 Monate
13. Männliche Patienten
14. Schwangerschaft oder Stillzeit
15. HER2-positiver Primärtumor oder HER2-positive Gewebeprobe einer metastatischen Läsion
16. Jede vorangegangene Behandlung mit anti-HER2-gerichteter Therapie

Randomisation

Patienten, die den Ein- und Ausschlusskriterien entsprechen, werden 1:1 auf die zwei Behandlungsarme randomisiert. Stratifizierung: Anzahl CTC (<5 vs. ≥5) und Therapielinie (1. vs. ≥1).

Patientenzahl

Die Fallzahlschätzung wurde unter folgenden Annahmen durchgeführt:

- Nachweis von CTCs in 65% der MBC Patientinnen
- Nachweis von HER2-positiven CTC in 20% der CTC positiven Patientinnen
- Randomisierung von 45% der Patientinnen mit HER2-positiven CTCs
- Nachweis einer Erhöhung des Anteils von Patientinnen, bei denen nach Chemotherapie keine CTCs im Blut mehr nachgewiesen werden können, von 54% im Kontrollarm auf 77% im experimentellen Arm (einseitiger Test, Type I Fehler 5%, Teststärke 80%).

Unter diesen Annahmen müssen insgesamt ca. N=2000 Patientinnen für DETECT III gescreent werden, um die benötigte Zahl von 120 Patientinnen in die Studie einschleusen zu können.

STUDIENABLAUF DETECT III

Visiten	**Screening-visite**	**Randomisationsvisite**	**Kontroll-visiten**	**Abschluss-visite**	**Follow-up-visiten**
Zeitpunkt	≤ 21 Tage vor Randomisations-visite	≤ 21 Tage nach Screening-visite	alle 3 oder 4 Wochen abhängig von der Standardtherapie	12 Monate nach 1. Dosis oder bei vorzeitigem Therapieabbruch (z.B. bei Progress)	2 bis 4 Wochen nach Abschluss-visite, dann alle 3 Monate
Zeitraum	**Vorbehandlung – Evaluationszeitraum**		**Randomisierte Behandlunsphase**		**Follow-Up-phase**
Pat.-Einverständnis Nr. 1 (Blutentnahme für CTC-Bestimmung und Bestimmung des HER2- Status auf den CTCs[1])	X				
Pat.-Einverständnis Nr. 2[1]		X			
Pat.-Einverständnis Nr. 3 (Blutentnahmen i.R. des translationalen Forschungsprojekts)[1,2]		X			
Vergabe der Patienten-Identifikationsnummer	X				
Demographische Daten (Geburtsjahr)*	X				
Datum der primären Tumordiagnose*	X				
Informationen über die primäre Brustkrebserkrankung (TNM*, Histologie*, Grading*, Lokalisation**, Operation**)	X				
Informationen über die Metastasen (Datum der Diagnose*, Lokalisation*, Operation**)	X				
HER2 Status des Primärtumors und/oder der Metastasen*	X				
Hormonrezeptorstatus des Tumorgewebes*	X				
Adjuvante/Neoadjuvante Therapie**	X				
Anzahl vorangegangener Chemotherapien in palliativer Situation*, Art der Therapien im metastasierten Stadium**	X				
Blutentnahme für die CTC-Bestimmung und die Bestimmung des HER2-Status der CTCs	X[5] *Screening-Kit*		X *Analyse Kit* nur bei den Kontrollvisiten alle 8-12 Wochen[20] nach Beginn der Therapie oder bei vorzeitigem Therapieabbruch (z.B. bei Progress)		
Blutentnahmen i.R. des translationalen Forschungsprojekts	X[6] *(im Screening-Kit enthalten)*	X *Analyse-Kit*			
Größe und Gewicht der Patientin		X			
Anamnese / Voroperationen		X			
Begleiterkrankungen		X			

Visiten	Screening-visite	Randomisationsvisite	Kontrollvisiten	Abschlussvisite	Follow-up-visiten
Andauernde Toxizitäten aufgrund vorangegangener antineoplastischer Therapien[3]		X			
Hormonrezeptorstatus des Tumorgewebes[4]	X				
Vorangegangene antineoplastische Medikation, andere relevante Vor-Medikation		X			
Begleitmedikation		X	X	X	X
Dokumentation und Prüfung der Eignung der geplanten Standard Chemo- oder endokrinen Therapie in Kombination mit Lapatinib		X[17]			
Behandlung gemäß Prüfplan (Standard Chemo- oder endokrine Therapie +/- Lapatinib)		X[18]	X	X[19]	
Vitalparameter (Herzfrequenz, Blutdruck, Körpertemperatur)		X	X	X	
Körperliche Untersuchung		X	X	X	
Unerwünschte Ereignisse		X	X	X	X
Blutbild[7]		X[9]	X	X	
Klinische Chemie[8]		X[9]	X	X	
Schwangerschaftstest im Serum oder Urin		X[9]			
Tumorbeurteilung gemäß der RECIST Leitlinien (Version 1.1)[12] (siehe Protokoll Abschnitt 10.2.1.)		X[16]	X[11]		
Tumormarker[21]		X	X		
12-Kanal EKG		X[10]			
UKG (inklusive LVEF-Bestimmung)		X[10]	X[14]	X	
Lebensqualität (EORTC QLQ-C30 und -BR23)		X[13]	X	X	
Schmerzintensität (NRS)		X	X	X	
Durchsicht der Ein- und Ausschlusskriterien		X			
Randomisierung		X			
Gabe von Denosumab			X[15]		
Ausgabe von Lapatinib		X			
Zusätzliche Ausgabe von Lapatinib falls notwendig			X		
Tablettenzählung (Lapatinib)			X	X	
Einsammeln der ungebrauchten Lapatinib-Tabletten				X	
Erinnerung der Patientin an die geplanten Follow-up Visiten				X	
Überleben			X	X	X

[1] vgl. Abschnitt 16.4
[2] Die Patientin kann auch an der Studie teilnehmen, wenn sie ihr Einverständnis hierfür nicht gegeben hat. In diesem Fall darf kein Material für das translationale Forschungsprojekt gesammelt und verwendet werden.
[3] vgl. Abschnitt 11.1
[4] Östrogen- und Progesteronstatus jeweils als positiv oder negativ eingestuft
[5] Das Ergebnis muss vor dem Randomisationsbesuch vorliegen. Die Blutentnahme zur Bestimmung von zirkulierenden Tumorzellen und Bestimmung des HER2-Status auf den CTCs sollte mit einem Mindestabstand von 1 Woche zu einer vorangegangenen antineoplastischen Therapie stattfinden.
[6] ggf.: zusätzliche Blutentnahme bei Patientinnen, die ihre Einwilligung zur Teilnahme am translationalen Forschungsprojekt gegeben haben (Bestandteil der Pat.-Info und der Einverständniserklärung Teil 1). Die dazugehörigen Blutröhrchen sind im Screening-Kit enthalten. Wenn eine Patientin diese Blutentnahme ablehnt, kann sie dennoch an der Studie teilnehmen.
[7] muss beinhalten: Hämoglobin, Hämatokrit, Zählung der Erythrozyten, Differentialblutbild, Zählung der Thrombozyten
[8] muss beinhalten: Bilirubin (total und direkt), ALT, AST, Albumin, Serum Kreatinin, Harnstoff, Natrium, Kalium, Calcium
[9] Ergebnisse dürfen nicht älter als 7 Tage sein
[10] Ergebnisse dürfen nicht älter als 3 Wochen sein
[11] Alle 8 bis 12 Wochen nach Beginn der palliativen Behandlung (je nach individuellem Behandlungsschema) oder falls medizinisch indiziert.
Im Fall einer endokrinen Behandlung: Kontrolle des Therapieansprechens alle 3 Monate oder falls medizinisch indiziert. Generell soll die Kontrolle des Therapieansprechens zusammen mit der Bestimmung der CTCs erfolgen.
[12] Bei jeder Beurteilung sollte dieselbe Methode verwendet werden.
[13] Ergebnisse dürfen nicht älter als 1 Woche sein
[14] nur wenn medizinisch indiziert
[15] Nur Patientinnen mit Knochenmetastasen: Xgeva®120 mg s.c. q4w. Zur Prävention einer Hypokalzämie sollten Calcium (mind. 500 mg p.o./Tag) und Vitamin D (mind. 400 I.E p.o./Tag.) verordnet werden.
[16] Ergebnisse dürfen nicht älter als 6 Wochen sein
[17] Keine Therapiegabe, jedoch Dokumentation der geplanten Standardtherapie und Prüfung, ob die Kombination mit Lapatinib zugelassen ist (vgl. SPC von Tyverb® 250 mg Tabletten) oder ob die Kombination in vorangegangenen Studien bereits untersucht wurde.
[18] Initiierung der Behandlung gemäß Prüfplan, d.h. Standardtherapie +/- Lapatinib innerhalb 1 Woche nach Randomisierung
[19] Dokumentation der Behandlung am Ende der randomisierten Phase (Standardtherapie +/- Lapatinib) und Dokumentation der geplanten Therapie im Anschluss
[20] Im Fall einer endokrinen Behandlung: CTC Bestimmung sollte alle 3 Monate erfolgen. Generell soll die Kontrolle des Therapieansprechens zusammen mit der Bestimmung der CTCs erfolgen.
[21] Tumormarker werden bei jeder Tumorevaluation bestimmt: CA15-3 obligat, CA125 und CEA optional

*Diese Daten müssen beim Screening-Visit erhoben werden. Eine Teilnahme am Screening ist ohne diese Daten nicht möglich.
**Die Patientin kann auch ohne Dokumentation dieser Daten gescreent werden. Die Erhebung und Dokumentation wird zusätzlich vergütet.
***Muss beim Screening vorliegen. Bei Patientinnen, bei denen keine standardmäßige HER2-Testung zum Zeitpunkt der Primärdiagnose verfügbar war und keine Biopsie einer metastatischen Läsion vorliegt, wird von einem HER2-negativen Primärtumor ausgegangen.

APPENDIX II – PATIENT EVALUATION FLOW SHEET

Visits	**Screening Visit**	**Randomization Visit**	**Control Visits**	**Conclusion Visit of Randomized Treatment Period**	**Follow-up Assessments**
Time	≤ 21 days prior to end of Randomization Visit	≤ 21 days after Screening Visit	q 3 or 4 weeks depending on standard treatment	12 months after first dose or at premature termination of protocol treatment (eg if PD)	2 to 4 weeks after Conclusion Visit, then q 3 months
Periods	**Pre-Treatment Evaluation Period**		**Randomized Treatment Period**		**Follow-Up Period**
Informed consent - part 1 in blood sampling for CTC count and HER2 status on CTC[1]	X				
Informed consent - part 2 in study participation[1]		X			
Informed consent - part 3 in blood sampling for translational medical investigations[1,2]		X			
Allocation of the patient identification number	X				
Demography (YOB)*	X				
Date of primary tumor diagnosis*	X				
Information on primary breast cancer (TNM*, histology*, grading*, localisation**, surgery**)	X				
Information on metastases (date of diagnosis*, localization*, surgery**)	X				
HER2 status on primary tumor tissue and/or biopsies from metastatic sites	X				
Hormone receptor status on primary tumor tissue and/or biopsies from metastatic sites*	X				
Adjuvant/Neoadjuvant Therapy**	X				
Number of prior chemotherapy lines for metastatic disease*, type of therapies for metastatic disease**	X				
Blood sampling for CTC count and assessment of HER2 status on CTC	X[5] *Screening Kit*		X *Analysis Kit* Only at visits scheduled every 8-12 weeks[20] after 1st dose or at premature discontinuation of protocol treatment (eg if PD)		
Blood sampling for translational medical investigations	X[6] (part of Screening Kit)	X *Analysis Kit*			
Patient height + weight		X			
Medical/surgical history		X			

Visits	Screening Visit	Randomization Visit	Control Visits	Conclusion Visit of Randomized Treatment Period	Follow-up Assessments
Concomitant diseases		X			
Ongoing toxicities attributed to prior anticancer therapies[3]		X			
Hormone receptor status in solid tumor tissue[4]	X				
Prior anticancer medication, other relevant prior medication		X			
Concomitant medication		X	X	X	X
Documentation of and check for compatibility of planned standard chemo- or endocrine therapy with lapatinib		X[17]			
Protocol treatment (standard chemo- or endocrine therapy +/-lapatinib)		X[18]	X	X[19]	
Vital signs (heart rate, blood pressure, temperature)		X	X	X	
Physical examination		X	X	X	
Adverse Events		X	X	X	X
Hematology[7]		X[9]	X	X	
Biochemistry[8]		X[9]	X	X	
Serum or urine pregnancy test		X[9]			
Tumor evaluation according to RECIST guidelines (version 1.1)[12] (see protocol section 10.2.1.)		X[16]	X[11]		
Tumor markers[21]		X	X		
12-lead ECG		X[10]			
UCG (including LVEF assessment)		X[10]	X[14]	X	
Quality of life (EORTC QLQ-C30 and -BR23)		X[13]	X	X	
Intensity of pain (NRS)		X	X	X	
Review of inclusion and exclusion criteria		X			
Randomization		X			
Application of denosumab			X[15]		
Dispense of lapatinib		X			
Additional supply of lapatinib if necessary			X		
Tablet count			X	X	
Collection of unused lapatinib				X	
Reminding the patient of the follow-up procedures planned				X	
Survival			X	X	X

[1]Cf. section 16.4

[2] Patient may participate in the study if this consent was not granted. However, in this case body material must not be sampled for the purpose of translational medical investigations

[3] Cf. section 11.1

[4] Estrogen and progesterone status each graded positive or negative

[5] Results must be obtained prior randomization visit. Blood sampling for CTC count and assessment of their HER2 status should be scheduled at least one week after last application of investigational agents of any type or anticancer therapy.

[6] 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.

[7] Must include: hemoglobin, hematocrit, red blood cell count, differential white blood cell count, platelet count

[8] Must include: total and direct bilirubin, ALT, AST, albumin, serum creatinine, BUN or urea, sodium, potassium, calcium

[9] Results obtained within the preceding 7 days may be employed

[10] Results obtained within the 3 preceding weeks may be employed

[11] Every 8 to 12 weeks after initiation of palliative treatment based on the individual treatment schedule or if medically indicated. In case of endocrine treatment therapy response evaluation should be performed every 3 months or if medically indicated. Treatment response evaluation should be performed together with the determination of CTCs

[12] The same method should be used on every assessment

[13] Results obtained within the preceding week may be employed

[14] Only if medically indicated

[15] Only in Patients with bone metastases: Xgeva®120 mg s.c. q4w; Administer calcium (at least 500 mg p.o. daily) and vitamin D (at least 400 I.E. p.o. daily) to prevent hypocalcemia.

[16] Results obtained within the 6 preceding weeks may be employed

[17] No administration of therapy, but documentation of planned standard therapy and check whether combination with lapatinib is either approved (see SPC of Tyverb® 250 mg tablets) or has been investigated in prior clinical trials.

[18] Initiation of protocol treatment, i.e. standard therapy +/- lapatinib within one week after randomization

[19] Documentation of end of protocol treatment (standard therapy +/-lapatinib therapy) and documentation of planned therapy after end of protocol treatment

[20] In case of endocrine treatment therapy CTC count should be performed every 3 months. Generally treatment response evaluation should be performed together with the determination of CTCs.

[21] Tumor markers are assessed on each tumor evaluation: CA15-3 is mandatory, CA125 and CEA are optional

*Data must be obtained before screening

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

APPENDIX III - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

In this clinical trial the ECOG-Score will be used only.

APPENDIX IV – NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 4.03 (CTCAE)

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE) for adverse events and serious adverse event reporting. A copy of the CTCAE Version 4.03 can be downloaded from the CTEP home page:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX V – QUALITY OF LIFE ASSESSMENTS

Introduction

Possible prolongation of survival due to additional treatment with lapatinib must be appraised in the light of contingent side effects, which may lower patients' quality of life. To evaluate eventual efficacy of lapatinib, quality of life assessments are indispensable.

Instructions for Administration of a Quality of Life Questionnaire.

The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

   The center CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that she prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

   The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, she should still complete the questionnaire prior to treatment.

   A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

   It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

4. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if she is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.
If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

5. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if she is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

6. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks one of the languages that the questionnaire may be available in, but does not wish to complete the questionnaires then she is NOT eligible and should NOT be put on study.

7. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the center clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

The Quality of Life Questionnaires

The Quality of Life Questionnaire to be applied in this clinical trial is the EORTC QLQ-C30, Version 3.0. In addition, the Breast Module EORTC QLQ-BR23, Version 1.0 is to be used. A German translation of both documents can be found below.

Patientin-Nr.: | | | | | | Zentrums-Nr.: | | | Geburtsjahr der Patientin: | | | |

Erhebung der Lebensqualität:

Das heutige Datum (Tag, Monat, Jahr): | | | | | |

Vor Randomisierung ☐ **Vor jeder Kontrollvisite** (alle 3-4 Wochen) ☐

Nach Abschluss der Studientherapie (Abschlussvisite) ☐

EORTC QLQ-C30

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine "richtigen " oder "falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

		Überhaupt nicht	Wenig	Mäßig	Sehr
1	Bereitet es Ihnen Schwierigkeiten, sich körperlich anzustrengen (z. B. eine schwere Einkaufstasche oder einen Koffer zu tragen)?	1	2	3	4
2	Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3	Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	1	2	3	4
4	Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5	Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:		Überhaupt nicht	Wenig	Mäßig	Sehr
6	Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7	Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8	Waren Sie kurzatmig?	1	2	3	4
9	Hatten Sie Schmerzen?	1	2	3	4
10	Mußten Sie sich ausruhen?	1	2	3	4
11	Hatten Sie Schlafstörungen?	1	2	3	4
12	Fühlten Sie sich schwach?	1	2	3	4
13	Hatten Sie Appetitmangel?	1	2	3	4
14	War Ihnen übel?	1	2	3	4

DETECT III

Patientin-Nr.: | | | | | | Zentrums-Nr.: | | | Geburtsjahr der Patientin: | | | |

Während der letzten Woche:	Überhaupt nicht	Wenig	Mäßig	Sehr
15 Haben Sie erbrochen?	1	2	3	4
16 Hatten Sie Verstopfung?	1	2	3	4
17 Hatten Sie Durchfall?	1	2	3	4
18 Waren Sie müde?	1	2	3	4
19 Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20 Hatten Sie Schwierigkeiten, sich auf etwas zu konzentrieren, z. B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21 Fühlten Sie sich angespannt?	1	2	3	4
22 Haben Sie sich Sorgen gemacht?	1	2	3	4
23 Waren Sie reizbar?	1	2	3	4
24 Fühlten Sie sich niedergeschlagen?	1	2	3	4
25 Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26 Hat Ihr körperlicher Zustand oder ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27 Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsame Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28 Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich getragen?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Wochen einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Wochen einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

DETECT III

Patientin-Nr.: | | | | | | Zentrums-Nr.: | | | Geburtsjahr der Patientin: | | | |

Erhebung der Lebensqualität:

Das heutige Datum (Tag, Monat, Jahr): | | | | | | |

Vor Randomisierung ☐ **Vor jeder Kontrollvisite** (alle 3-4 Wochen) ☐

Nach Abschluss der Studientherapie (Abschlussvisite) ☐

EORTC QLQ-BR23

Patientinnen berichten manchmal die nachfolgend beschriebenen Symptome oder Probleme. Bitte beschreiben Sie wie stark Sie diese Symptome oder Probleme währen der letzten Woche empfunden haben.

Während der letzten Woche:	Überhaupt nicht	Wenig	Mäßig	Sehr
31 Hatten Sie einen trockenen Mund?	1	2	3	4
32 War Ihr Geschmacksempfinden beim Essen oder Trinken verändert?	1	2	3	4
33 Schmerzten Ihre Augen, waren diese gereizt oder tränten sie?	1	2	3	4
34 Haben Sie Haarausfall?	1	2	3	4
35 *Nur bei Haarausfall ausfüllen:* Hat Sie der Haarausfall belastet?	1	2	3	4
36 Fühlten Sie sich krank oder unwohl?	1	2	3	4
37 Hatten Sie Hitzewallungen?	1	2	3	4
38 Hatten Sie Kopfschmerzen?	1	2	3	4
39 Fühlten Sie sich wegen Ihrer Erkrankung oder Behandlung körperlich weniger anziehend?	1	2	3	4
40 Fühlten Sie sich wegen Ihrer Erkrankung oder Behandlung weniger weiblich?	1	2	3	4
41 Fanden Sie es schwierig, sich nackz anzusehen?	1	2	3	4
42 Waren Sie mit Ihrem Körper unzufrieden?	1	2	3	4
43 Waren Sie wegen Ihres künftigen Gesundheitszustandes besorgt?	1	2	3	4

DETECT III

Patientin-Nr.: | | | | | | Zentrums-Nr.: | | | Geburtsjahr der Patientin: | | | |

Während der letzten vier Wochen:	Überhaupt nicht	Wenig	Mäßig	Sehr
44 Wie sehr waren Sie an Sex interessiert?	1	2	3	4
45 Wie sehr waren Sie sexuell aktiv?	1	2	3	4
46 *Nur ausfüllen, wenn Sie sexuell aktiv waren*: Wie weit hatten Sie Freude am Sex?	1	2	3	4

Während der letzten Woche:	Überhaupt nicht	Wenig	Mäßig	Sehr
47 Hatten Sie Schmerzen in Arm oder Schulter?	1	2	3	4
48 War Ihr Arm oder Ihre Hand geschwollen?	1	2	3	4
49 War das Heben oder Seitwärtsbewegen des Arms erschwert?	1	2	3	4
50 Hatten Sie im Bereich der betroffenen Brust Schmerzen?	1	2	3	4
51 War der Bereich Ihrer betroffenen Brust angeschwollen?	1	2	3	4
52 War der Bereich der betroffenen Brust überempfindlich?	1	2	3	4
53 Hatten Sie Hautprobleme im Bereich der betroffenen Brust (z.B. juckende, trockende oder schuppende Haut)?	1	2	3	4

DETECT III

APPENDIX VI – PROHIBITED MEDICATIONS

Drug class	Agent	**Wash-out** (period of time that the medication should be discontinued prior to administration of the first dose of protocol treatment)*
Inducers of CYP3A4		
Antibiotics	All rifamycin class agents (rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	Phenytoin, carbamazepine, barbiturates (phenobarbital)	14 days
Antiretrovirals	Efavirenz, nevirapine, tipranivir, etravirine	14 days
Glucocorticoids (oral) (premedication before the administration of taxanes is allowed)	Chronic use of cortisone (> 50mg), hydrocortisone (> 40 mg), prednisone or prednisolone (> 10 mg), methylprednisolone or triamcinolone (> 8 mg), betamethasone or dexamethasone (> 1.5 mg). Glucocorticoid daily doses (oral) ≤ 1.5 mg dexamethasone (or equivalent) are allowed. Short term steroid use (up to 2 weeks) is allowed**.** Premedication for taxane treatment is permitted.	14 days
Other	St. John's Wort, modafinil	14 days
Inhibitors of CYP3A4		
Antibiotic	clarithromycin, erythromycin, troleandomycin, flucloxacillin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (> 150 mg daily), voriconazole	7 days
Antiretrovirals, Protease Inhibitors	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinivir, atazanavir	7 days
Calcium channel blockers	verapamil, diltiazem	7 days
Antidepressants	nefazodone, fluvoxamine	7 days
GI Agents	Cimetidine**, aprepitant	7 days
Other	Grapefruit, grapefruit juice, star fruit, papaw amiodarone	7 days 6 months
Substrates of CYP2C8, Pgp, BCRP and OATP1B1		
Antidiabetics	Repaglinide	1 day
Statins	Rosuvastatine	1 week
Cardiac glycosides	Digoxin, digitoxin	2 weeks
Miscellaneous		
Antacids	Magnesium and aluminium hydroxide, simethicone, calcium carbonate, magnesium carbonate	1 hour before and after dosing
Herbal or dietary supplements and traditional Chinese medicines	Ginkgo biloba, kava, grape seed, valerian, ginseng, *Echinacea*, evening primrose oil.	14 days

* All patients must have observed the specified washout period for all prohibited drugs prior to randomization. However if the patient is randomized to the lapatinib arm then it is acceptable for the Investigator to restart the medications

** Note: cimetidine may be used as taxane pre-medication if this is the local institutional practice

APPENDIX VII – NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity				
Class	Cardiac Symptoms	Limitations	Need for Additional Rest *	Physical Ability to Work **
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.
Reference: Bruce, RA: Mod Concepts Cardiovasc Dis 25:321, 1956. (Modified from New York Heart Association, 1953)

APPENDIX VIII –ALGORITHM FOR LVEF ASSESSMENT AND LAPATINIB TREATMENT

Algorithm for LVEF assessment and lapatinib treatment in patients with cardiac adverse events based on assessment results of LVEF and NYHA status (see APPENDIX VII – NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE):

Asymptomatic cardiac events (NYHA I):
Subjects who have a ≥ 20% decrease in left ventricular cardiac ejection fraction relative to baseline, and the ejection fraction is below the institution's lower limit of normal, should have a repeat evaluation of ejection fraction 1-2 weeks later while still receiving investigational product.

- If the repeat ejection fraction evaluation confirms a ≥ 20% decrease in left ventricular cardiac ejection fraction, and the ejection fraction is below the institution's lower limit of normal, then investigational product should be temporarily discontinued.
  - If the left ventricular ejection fraction recovers during the next 3 weeks, after consultation and approval of the medical monitor, the subject may be restarted on investigational product at a reduced dose. For such subjects, monitoring of left ventricular ejection fraction will then be performed 2 weeks and 4 weeks after rechallenge, and then every 4 weeks thereafter.
  - If repeat ejection fraction evaluation still shows a decrease ≥ 20% in left ventricular ejection fraction relative to baseline, and the value is below the institution's lower limit of normal, then the subject should be withdrawn from investigational product.

Symptomatic cardiac events (NYHA II-IV):
Subjects with an NCI CTCAE grade 3 or 4 LVEF relative decrease must be withdrawn from study medication.

Cardiological consultation:
In general, it is strongly recommended that patients who have symptomatic decreases in LVEF or those who meet the criteria for stopping treatment seek cardiological consultation for advice on potential treatment for their cardiac dysfunction. Furthermore, in patients who permanently discontinue lapatinib due to cardiac toxicity, cardiac evaluations should be performed as clinically indicated, ideally every 4 weeks for at least 16 weeks or until resolution.

APPENDIX IX – DIARRHEA MANAGEMENT GUIDELINES

Diarrhea Management Guidelines for Investigator Sponsored Studies

Background

Experience thus far suggests that when lapatinib is used as monotherapy 51% of patients experience diarrhea; most diarrhea presents as uncomplicated NCI CTCAE Grade 1 or 2 (G1 30%, G2 15%, G3 6%, G4<1%) (Crown, 2008).

In rare cases, diarrhea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency, and/or electrolyte imbalances.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea (Benson, 2004). Presented in the sections below are the recommended guidelines for the management of diarrhea in subjects receiving lapatinib-based therapy; these guidelines were derived from the recommendations published by the ASCO panel (Benson, 2004).

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel patterns should be established so that changes in patterns can be identified while subject is on treatment.

It is strongly recommended to give subjects receiving lapatinib-based therapy a prescription of loperamide with instructions to start loperamide at the onset of diarrhea as per the recommendations outlined below.

Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity.

An assessment of frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently subjects at high risk of diarrhea can be identified. Subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physician.

It is recommended that subjects keep a diary and record the number of diarrhea episodes and its characteristics. They should also include information on any dietary changes or other observations that may be useful in the evaluation of their diarrhea history.

If subjects present with diarrhea of any Grade, check they are taking lapatinib correctly, i.e. single daily dose, rather than splitting it through the day. Obtain information on food (solid and liquid) and over the counter (OTC) medication, including herbal supplements, taken during the lapatinib treatment period.

Definitions

National Cancer Institute (NCI) guidelines define diarrhea compared to baseline (Table 1).

Table 1: NCI Common Terminology Criteria for Grading Diarrhea Adverse Events[1]

Adverse Event Grade	Diarrhea
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline;
3	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living (ADL)
4	Life-threatening consequences; urgent intervention indicated
5	Death

[1] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

Uncomplicated diarrhea is considered mild-to-moderate and defined as CTCAE Grade 1 or 2 with no complicating signs or symptoms.

Complicated diarrhea is severe and defined as any CTCAE Grade 3 or 4 diarrhea, or Grade 1 or 2 with one or more of the following signs or symptoms:

- Moderate to severe abdominal cramping

- Nausea/vomiting ≥Grade 2
- Decreased performance status
- Fever
- Sepsis
- Neutropenia
- Frank bleeding (red blood in stool)
- Dehydration

Management Guidelines for Subjects Receiving Lapatinib Alone or as Combination Therapy

A) Uncomplicated Diarrhea

I. CTCAE Grade 1

NOTE: Subject should be instructed to: start supportive care immediately at the first episode of diarrhea (i.e., unformed stool) and call their physician.

1. Administer loperamide*
    a. Initial dose 4 mg followed by 2 mg after every unformed stool. Re-evaluate after 24 hours, if:
        i. Diarrhea is resolving:
        - Continue loperamide treatment at 2 mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours.
            - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns
        ii. Diarrhea is not resolving:
        - Administer loperamide at 2 mg every 4 hours for the next 24 hour. Re-evaluate after 24 hours. If diarrhea is resolving, administer loperamide at 2mg after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours. If diarrhea is not resolving continue loperamide treatment at 2 mg every 4 hours and re-evaluate every 24 hours.
    b. If Grade 1 diarrhea persists for more than 1 week with loperamide treatment, consider treatment with second-line agents (i.e., octreotide, budesonide or tincture of opium).

2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):
    a. Stop all lactose containing products and eat small meals
    b. Avoid spicy, fried and fatty foods, raw vegetables and other foods high in fiber
        - Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
    c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
    d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
        - Avoid acidic drinks such as tomato juice and fizzy soft drinks
    e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots), evaluate their impact on diarrhea due to the fiber content (e.g., apricots)

3. Continue with study treatment (i.e., lapatinib-based treatment)

Continue with supportive care until diarrhea has resolved (diarrhea free for 12 hours/bowel pattern return to baseline). Once diarrhea has resolved, the subject can begin to gradually re-introduce foods from their normal diet.

If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications. Continue with study treatment.

If Grade 1 diarrhea persists for ≥2 weeks, refer to the management guidelines for Persistent Grade 2 Diarrhea.

II. CTCAE Grade 2

NOTE: Subject should be instructed to call physician at first episode of diarrhea and start supportive care immediately

1. Administer loperamide*
   a. Initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool. Re-evaluate after 24 hours. If:
      i. Diarrhea is resolving, continue loperamide treatment at 2 mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours
         - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns
      ii. Diarrhea is not resolving, consider loperamide dose of 2 mg every 2 hours for 24 hours. If Grade 2 diarrhea persists after total of 48 hours of loperamide treatment, start second-line agents (i.e., octreotide, budesonide or tincture of opium).
         - Consider performing stool work-up, CBC, electrolytes and other tests as appropriate

2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):
   a. Stop all lactose containing products and eat small meals
   b. Avoid spicy, fried and fatty foods, bran, raw vegetables and other foods high in fiber
      - Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
   c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
   d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
      - Avoid acidic drinks such as tomato juice and fizzy soft drinks
   e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots), evaluate their impact on diarrhea due to the fiber content (e.g., apricots)

3. Continue with study treatment (i.e., lapatinib-based treatment)

Continue with supportive care until diarrhea has resolved (diarrhea free for 12 hours/bowel pattern return to baseline). Once diarrhea has resolved, the subject can begin to gradually re-introduce foods from their normal diet. Refer to Section IV "Recurrent Diarrhea" for study treatment guidelines.

If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications.

III. Persistent (≥ 3days/72 hours) Grade 2 Diarrhea: hold lapatinib and chemotherapy (if applicable) until diarrhea resolves (<Grade 1/return to baseline bowel pattern).

1. If supportive care measures and the interruption of study treatment (i.e., lapatinib and if applicable chemotherapy) are ineffective in treating persistent Grade 1 or Grade 2 diarrhea, perform stool work-up, CBC, electrolytes and other tests as appropriate, consider consulting with a gastrointestinal (GI) specialist.

   a) After diarrhea resolves (<Grade 1/return to baseline bowel pattern), resume treatment with lapatinib and chemotherapy (if applicable).

IV. Recurrent Diarrhea (more than 1 occurrence of Grade 2 diarrhea): once the 2nd occurrence of Grade 2 diarrhea resolves to ≤Grade 1, consider reducing the dose of lapatinib by 250 mg or 1 tablet, unless the lapatinib dose already had been reduced to 750 mg. No further dose reduction is recommended for subjects taking lapatinib at 750 mg.

1. Consider a dose reduction for chemotherapy (if applicable)

B) Complicated Diarrhea

I. CTCAE Grade 3 or Grade 1 or 2 with complicating features (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration)

1. Subject **must** call physician immediately for any complicated severe diarrhea event
2. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4 mg followed by 2 mg every 2 hours or after every unformed stool*****
3. Refer to the dietary modification recommendations for Grade 1 and Grade 2 uncomplicated diarrhea
4. For dehydration use intravenous fluids as appropriate, if subject presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolytes and other tests as appropriate
6. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia
7. Hold lapatinib and chemotherapy (if applicable) until symptoms resolve to ≤Grade 1 (without complicating features) and reintroduce lapatinib at a reduced dose (unless dose had been reduced to 750 mg). Consider a dose reduction for chemotherapy (if applicable).
8. Supportive care and other interventions should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
9. Intervention may require hospitalization for subjects most at risk for life threatening complications

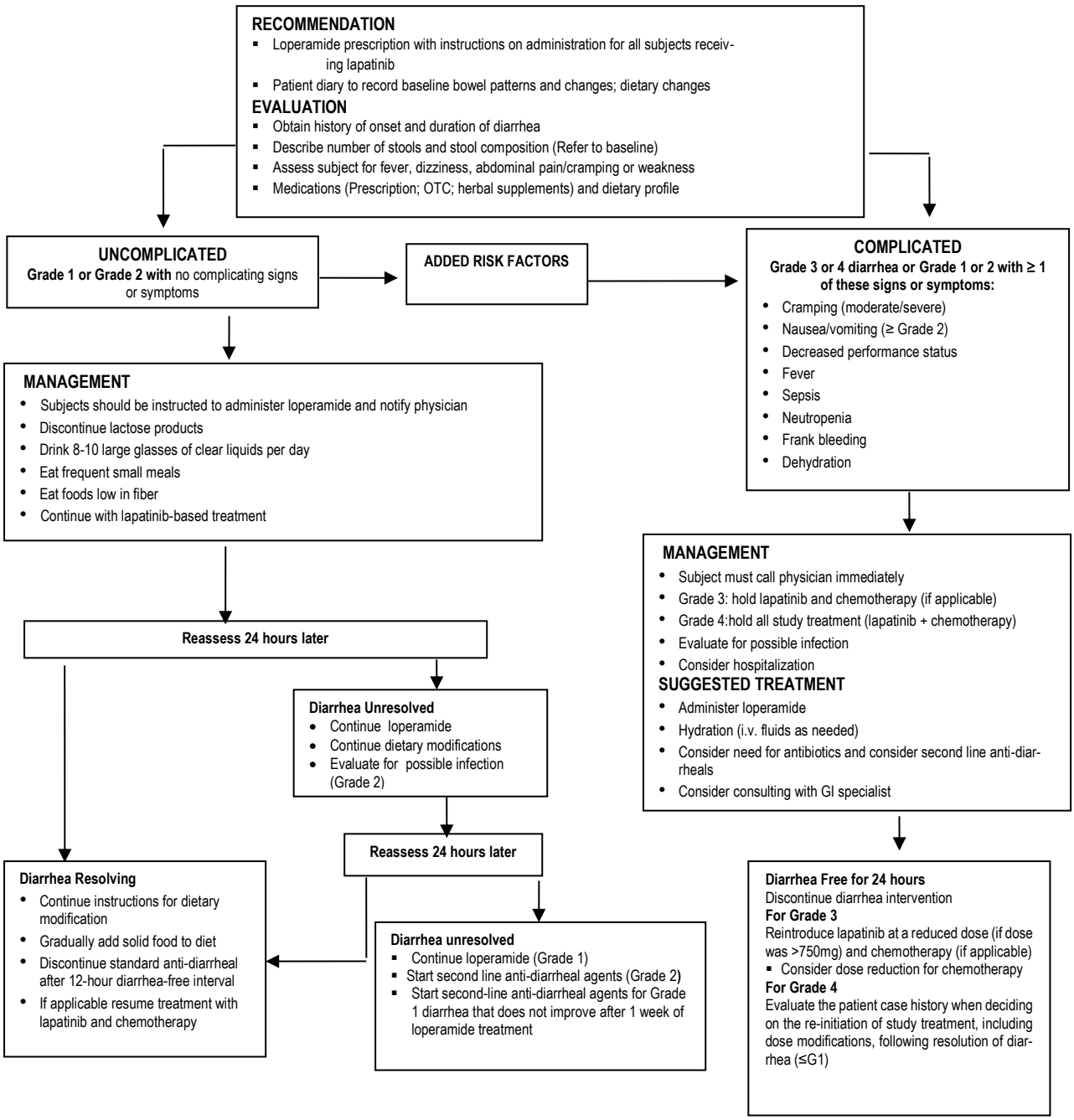
II. CTCAE Grade 4

1. Subject must call physician immediately for any Grade 4 diarrhea event
2. Hold treatment with lapatinib, hold chemotherapy or other concurrent anticancer therapy (if applicable)
    - Evaluate the patient case history when deciding on the re-initiation of study treatment, including dose modifications, following resolution of diarrhea (≤Grade 1)
3. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4 mg followed by 2 mg every 2 hours or after every unformed stool*****
4. For dehydration use intravenous fluids as appropriate, if subject presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolyte and other tests as appropriate
6. Recommend consulting with GI specialist
7. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3/4 neutropenia
8. Supportive care and other intervention should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
9. Intervention may require hospitalization for subjects most at risk for life threatening complications

*****It is recommended that the maximum cumulative daily dose of loperamide follows local guidance

Refer to and follow the recommended supportive care guidelines in the previous sections and as depicted in Figure 1

Figure 1: Algorithm for the management of diarrhea in subjects treated with lapatinib-based therapy



1. For Grade 1 diarrhea that persists for 2 weeks or longer, refer to Section III
2. For Grade 2 diarrhea that persists longer than 3 days/72 hours, refer to Uncomplicated Diarrhea Section III
3. For recurrent diarrhea, refer to Uncomplicated Diarrhea Section IV for further management guidelines

References

American Cancer Society. Coping with physical and emotional changes: Diarrhea: what the subject can do. Di-ahttp://www.cancer.org/docroot/MBC/content/MBC_2_3X_Diarrhea.asp

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Charma R, Tobin P, Clarke SJ. Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhea. Lancet/Oncology 2005; 6:93-102

Crown JP, Burstein HA, Boyle F, et al. Pooled analysis of diarrhea events in patients with cancer treated with lapatinib. Breast Cancer Res Treat 2008; 112:317-325.

Saltz LB. Understanding and Managing Chemotherapy-Induced Diarrhea. Journal of Supportive Oncology 2003; 1:35-46.

National Cancer Institute. Nutrition in cancer care (PDQ®). http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition/Subject

National Comprehensive Cancer network (NCCN). NCCN Clinical Practice Guidelines in Oncology. http://www.nccn.org

APPENDIX X – PATIENT ID CARD

<table>
<tr><td>EudraCT-Nr.: 2010-024238-46
Protocol Nr.: D-III
Sponsor:
Universitätsklinikum Ulm (AöR), Albert-Einstein-Allee 29, 89081 Ulm
Prof. Dr. W. Janni, Tel.: +49 (0) 731 500 58501</td><td>Im Notfall oder bei Einweisung in ein Krankenhaus zeigen Sie diese Karte bitte dem behandelnden Arzt</td></tr>
<tr><td>Name der Patientin:</td><td rowspan="2">Die Patientin erhält eine Behandlung mit (Standardtherapie):
_____
_____
☐ und zusätzlich _____ Tabletten (_____mg) Lapatinib/Tag
☐ ohne zusätzliches Lapatinib
Werden weitere Informationen benötigt, wenden Sie sich bitte an nebenstehende Telefonnummer.</td></tr>
<tr><td>...nimmt an folgender klinischen Prüfung teil
DETECT III: Multizentrische, randomisierte Phase III Studie zum Vergleich von Standardtherapie allein und Standardtherapie mit zusätzlichem Lapatinib bei initial HER2-negativem frühem Brustkrebs, aber HER2-positiven zirkulierenden Tumorzellen</td></tr>
<tr><td>Prüfzentrum:</td><td rowspan="2">Einnahmevorschrift für Lapatinib:
_____ Tabletten zur gleichen Zeit einmal täglich mit einem Glas Wasser nicht weniger als eine Stunde vor oder mindestens eine Stunde nach einer Mahlzeit einnehmen.
Bei Erbrechen kurz nach einer Einnahme diese nur wiederholen, wenn alle Tabletten erbrochen wurden, intakt sind und gezählt werden konnten.
Patienten, die mit Lapatinib behandelt werden, dürfen grundsätzlich nicht Grapefruit oder Grapefruitsaft zu sich nehmen.</td></tr>
<tr><td>Prüfarzt:

Telefon:</td></tr>
</table>

APPENDIX XI – DRAFT LABEL FOR IMP LAPATINIB

ACHTUNG: PRÜFMEDIKATION - ZUR KLINISCHEN PRÜFUNG BESTIMMT

DETECT III

Titel/StudienNr: DETECT III (D-III)
EudraCT-Nr. 2010-024238-46
Clinicaltrials.gov-ID: NCT01619111

90 Lapatinib 250 mg Filmtabletten zum Einnehmen.

Geburtsjahr: Patienten-Nr.: Zentrums-Nr.:

Wie verordnet einnehmen. Nicht zusammen mit Grapefruit oder Grapefruitsaft einnehmen.
Bitte sämtliche nicht verbrauchte Medikation zum nächsten Termin mitbringen.

Ch.-B.: ----- Verwendbar bis: --.--.----

Nicht über 30°C lagern. Vor Lichteinwirkung schützen.
ARZNEIMITTEL FÜR KINDER UNZUGÄNGLICH AUFBEWAHREN
Sponsor: Universitätsklinikum Ulm, Frauenklinik, Prittwitzstr. 43, 89075 Ulm, Prof. Dr. W. Janni, Tel.: +49 (0)731 500-58501

After the end of the transition period of up to 9 month, Novartis Pharma GmbH, D-90429 Nürnberg is responsible for provision of the IMP lapatinib. Each bottle containing tablets with lapatinib will be labeled as follows:

- Warning: “Handelsware – zur klinischen Prüfung bestimmt”

APPENDIX XII – ASSESSMENT OF PAIN INTENSITY

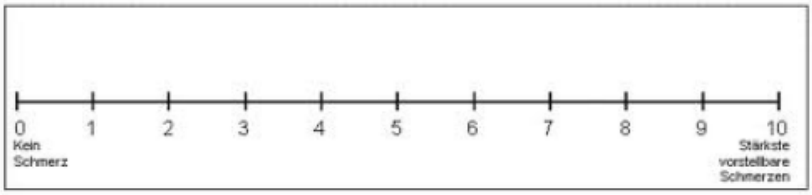
Possible relief of tumor associated pain due to different treatment regimen needs to be evaluated. To assess the pain intensity a numeric rating scale (NRS) is used.

Patientin-Nr.: | | | | | | Zentrums-Nr.: | | | Geburtsjahr der Patientin: | | | |

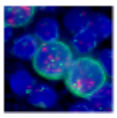
Schmerzevaluation:

Visitendatum: | | | | | |

Bitte markieren Sie auf der Skala die Schmerzintensität:



DETECT III



DETECT III

Informationsblatt: Behandlung mit Lapatinib (Tyverb®)

Lapatinib (Tyverb®) ist ein Wirkstoff zur Behandlung von Brustkrebs. Es hemmt einen Eiweißstoff mit der Bezeichnung HER2/neu (Erb2). HER2/neu wird bei manchen Brustkrebsarten auf der Oberfläche der Tumorzellen vermehrt ausgebildet und begünstigt ihr unkontrolliertes, schädigendes Wachstum.

Obgleich das Gewebe Ihres Tumors und/oder der Tochtergeschwülste (Metastasen) diesen Eiweißstoff HER2/neu nicht aufweist/aufgewiesen hat, konnten wir in Ihrem Blut Tumorzellen nachweisen, die HER2/neu ausbilden. Daher wird angenommen, dass Sie von einer HER2/neu-Hemmung durch Lapatinib profitieren, indem das Fortschreiten der Brustkrebserkrankung aufgehalten wird.

Anwendung von Lapatinib (Tyverb®)
Die Lapatinib-Dosis, die Sie erhalten, muss individuell eingestellt werden, da sie von der gleichzeitig verabreichten Standard Chemo- oder Antihormontherapie abhängt. Aus Sicherheitsgründen erhalten Sie nur eine Dosiskombination, die bereits für die Behandlung zugelassen ist, oder die schon einmal in einer anderen klinischen Studie untersucht worden ist. Es kann erforderlich sein, die Dosis im Verlauf der Therapie anzupassen. So kann sie bei Nebenwirkungen verringert oder nach Beendigung der Standardtherapie erhöht werden
Welche Dosis Sie einnehmen müssen teilt Ihnen Ihr Prüfarzt persönlich mit. Lapatinib wird in Form von Tabletten fortlaufend täglich eingenommen. Eine einzelne Tablette enthält 250 mg Lapatinib. Um auf die gewünschte Dosis zu kommen, müssen Sie also eine entsprechende Anzahl Tabletten einnehmen:

- 750 mg/Tag = 3 Tabletten
- 1000 mg/Tag = 4 Tabletten
- 1250 mg/Tag = 5 Tabletten
- 1500 mg/Tag = 6 Tabletten

Die **Einnahme** sollte folgendermaßen erfolgen:

- einmal täglich fortlaufend
- zur selben Tageszeit
- eine Tablette nach der anderen mit einem Glas Wasser
- mindestens 1 Stunde vor oder 1 Stunde nach der Mahlzeit

Bitte beachten Sie folgende **Hinweise**:

- Lapatinib-Tagesdosis nicht aufteilen
- falls Sie eine Einnahme vergessen haben, nehmen Sie keine doppelte Tablettendosis ein.
- trinken Sie während der Therapie mit Lapatinib keinen Grapefruitsaft. Er kann auf die Medikamente störend einwirken. Achten Sie in diesem Zusammenhang auch auf „versteckte" Inhaltsstoffe: so kann z.B. in einem Multivitaminsaft auch Pampelmuse/Grapefruit enthalten sein.
- Die gemeinsame Behandlung mit Lapatinib und bestimmten anderen Medikamenten sollte aufgrund von Wechselwirkungen unbedingt vermieden werden. Besprechen Sie vor Beginn der Therapie mit Lapatinib die Einnahme anderer Arzneimittel (inkl. pflanzlicher und/oder nicht verschreibungspflichtiger Präparate) mit Ihrem Prüfarzt.

Bei Ihren Besuchen im Prüfzentrum werden Sie jeweils so mit Lapatinib-Tabletten versorgt, dass Sie ausreichend Tabletten bis zum nächsten Besuch haben. Sie erhalten Lapatinib in Flaschen mit je 90 Tabletten.

Maßnahmen beim Auftreten von Nebenwirkungen durch Lapatinib (Tyverb®)
Wie alle Arzneimittel kann Lapatinib Nebenwirkungen hervorrufen, die aber nicht bei jedem auftreten müssen. Hier geben wir Ihnen Anweisungen, was Sie bei Nebenwirkungen tun können:

Durchfall
Wichtig: Benachrichtigen Sie umgehend Ihren behandelnden Prüfarzt beim ersten Auftreten von Durchfall.

- Trinken Sie ausreichend Wasser, 8-10 Gläser z.B. Mineralwasser oder isotonische Sportgetränke
- Vermeiden Sie fettige und scharf gewürzte Speisen. Stattdessen sollte Ihr Essen aus fettarmen Mahlzeiten mit hohem Eiweißanteil bestehen (z.B. mageres Fleisch oder Eier)
- Vermeiden Sie Milch und Milchprodukte
- Vermeiden Sie sowohl koffeinhaltige als auch alkoholhaltige Getränke
- Essen Sie statt rohem Gemüse gekochtes Gemüse, und entfernen Sie die Schale von Obst
- Nach Rücksprache mit Ihrem behandelnden Prüfarzt: nehmen Sie bei akuten Durchfällen zu Beginn der Behandlung 2 Kapseln Loperamid (= 4mg), danach 1 Kapsel (= 2 mg) alle 4 Stunden oder nach jedem flüssigen Stuhl. Täglich dürfen Sie nicht mehr als 8 Kapseln (= 16 mg) einnehmen

Hautausschläge

- Waschen Sie sich mit lauwarmen Wasser
- Verwenden Sie milde, pH-neutrale Waschlotion
- Achten Sie auf regelmäßige, konsequente Hautpflege
- Benutzen Sie Sonnencreme (mind. Lichtschutzfaktor 30), meiden Sie direktes Sonnenlicht und tragen Sie bedeckende Kleidung
- Verwenden Sie parfümfreie hypoallergene Hautcremes oder Make-up für empfindliche Haut (Apotheke).
- Tragen Sie bei Haus- oder Gartenarbeit Handschuhe

Wichtig: Benachrichtigen Sie umgehend Ihren behandelnden Prüfarzt.

Übelkeit

- Essen Sie bevor Sie sich hungrig fühlen
- Essen Sie mehrere kleine Mahlzeiten pro Tag
- Vermeiden Sie zu heiße oder zu kalte Nahrung
- Gehen Sie in ein anderes Zimmer, falls Sie Kochgerüche stören
- Vermeiden Sie Fettiges, sehr Süßes oder Scharfes

Erbrechen

- Vermeiden Sie bestimmte Speisen oder Gerüche, bei denen Ihnen übel wird, oder Situationen, die bei Ihnen Reisekrankheit auslösen können (z.B. Auto fahren)
- Essen und trinken Sie nichts bis es Ihnen wieder besser geht
- Starten Sie mit kleinen Mengen klarer Getränke (z.B. stilles Mineralwasser). Wenn Sie dieses bei sich behalten können, versuchen Sie milde Speisen wie Haferbrei, Joghurt, klare Suppen etc. Nehmen Sie dann Schritt für Schritt wieder festere Nahrung zu sich. Manchmal hilft auch Ingwer gegen Übelkeit und Entzündungen (ca. 1 cm frischen Ingwer zerdrücken und in 0,2 Liter kochendem Wasser 10 Minuten ziehen lassen und abseihen).

Schwächegefühl

- Setzen Sie sich realistische Ziele, was Sie an einem Tag schaffen können
- Verteilen Sie Ihre Aktivitäten gleichmäßig über den Tag. Machen Sie zwischendurch Pausen.
- Bewegen Sie sich nach Ruhepausen regelmäßig, um wieder in Schwung zu kommen.
- Sprechen Sie mit Ihrem Prüfarzt, bevor Sie mit Sportaktivitäten beginnen.
- Und vor allem: Machen Sie viele Dinge, die Ihnen Spaß machen und guttun.

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DETECT III

Informationsblatt: Behandlung mit Denosumab (Xgeva®)

Sind bei Ihrer Brustkrebserkrankung Tochtergeschwülste (Metastasen) in den Knochen festgestellt worden, so ist eine medikamentöse Therapie vorgesehen. Diese soll die Knochenschädigung aufhalten und das Risiko von Knochenbrüchen verringern.

Sie erhalten im Rahmen der DETECT III Studie zusätzlich zur Standard Chemo-/Antihormontherapie (mit/ohne Lapatinib (Tyverb®)) das Medikament mit dem Handelsnamen Xgeva®. Der darin enthaltene Wirkstoff Denosumab ist zugelassen für die Behandlung von erwachsenen Patienten/-innen mit Knochenmetastasen und wird in der Studie entsprechend der aktuellen Fachinformation angewendet.

Wirkung von Denosumab (Xgeva®)
In einem gesunden Organismus finden im Knochen stetig Erneuerungsprozesse statt. Dabei herrscht ein Gleichgewicht zwischen knochenbildenden Knochenzellen (= Osteoblasten) und knochenabbauenden Knochenzellen (= Osteoklasten). Dieses Gleichgewicht wird durch die Anwesenheit von sich vermehrenden Krebszellen gestört. Wenn der Abbau des Knochens überwiegt, kann es zu einer Beeinträchtigung der Stabilität und damit auch zu Knochenbrüchen kommen. Denosumab ist ein Antikörper der die knochenabbauenden Zellen hemmt und so den weiteren Abbau von Knochensubstanz verhindert.

Anwendung von Denosumab (Xgeva®)
Denosumab (Xgeva®) wird Ihnen alle 4 Wochen in Form einer einzelnen Spritze unter die Haut (subkutan) entweder in den Oberschenkel, den Bauch oder in den Oberarm verabreicht.

Nebenwirkungen von Denosumab (Xgeva®)
Unter der Therapie mit Denosumab (Xgeva®) kann es zu folgenden Nebenwirkungen kommen:

- Hautreizungen → Symptome: Juckreiz und Rötung der Haut
- Niedriger Kalziumspiegel: sehr selten wurde unter der Therapie mit Denosumab ein vorübergehender Abfall der Kalziumwerte im Blut unter den Normalbereich beobachtet, vereinzelt mit tödlichem Ausgang → Symptome: Kribbeln, Muskelkrämpfe, abnormaler Herzschlag
  Dem Abfall des Kalziumspiegels im Blut kann entgegengewirkt werden, in dem Sie Kalzium und Vitamin D so einnehmen, wie es Ihnen Ihr Prüfarzt verordnet hat
- Krankhafter Abbau des Kieferknochens (Kieferosteonekrose): in sehr seltenen Fällen kann sich Denosumab durch eine verminderte Durchblutung negativ auf den Kieferknochen auswirken → Symptome: Schmerzen oder Infektion des Zahnfleischs, Zahnlockerung, Schmerzen im Kieferbereich
- Atypische Oberschenkelfrakturen: sehr selten sind unter der Denusomab-Therapie Frakturen nach geringem oder ohne Trauma aufgetreten, häufiger beidseitig → Symptome: neu auftretende oder ungewöhnliche Oberschenkel-, Hüft- oder Leistenschmerzen

Wichtig: Falls bei Ihnen während der Behandlung mit Denosumab o.g. Symptome auftreten, sollten Sie Ihren Prüfarzt unverzüglich benachrichtigen.

Kieferknochennekrose: Vorsichtsmaßnahmen vor und während der Therapie mit Denosumab (Xgeva®)
In sehr seltenen Fällen kann es zu einer Kieferknochennekrose kommen. Sie sollten unter der Therapie mit Denosumab folgende Punkte beachten:

- Lassen Sie vor Beginn der Behandlung mit Denosumab Ihre Zähne professionell untersuchen, reinigen und wiederholen Sie dies auch während der Therapie alle 6 Monate.

- Weisen Sie Ihren Zahnarzt auf die geplante Therapie hin (Chemotherapie, Denosumab). Eventuell notwendige Zahnbehandlungen sollten abgeschlossen sein. Vor einer invasiven Zahnbehandlung und/oder einem kieferorthopädischen Eingriff sollte eine Therapie mit Denosumab mindestens 30 Tage pausiert sein. Eine Wiederaufnahme der Therapie sollte erst dann erfolgen, wenn die Mundschleimhaut vollständig ausgeheilt ist.

- Achten Sie auf eine gründliche Mund- und Zahnhygiene (siehe unten).

- Achten Sie bitte auf folgende Symptome:
  Schmerzen, Anschwellung oder Infektion des Zahnfleischs, Zahnlockerung, Schmerzen im Kieferbereich.
  Wenn diese oder andere Symptome der Zähne auftreten, berichten Sie dies bitte sofort Ihrem betreuenden Studienarzt und Ihrem Zahnarzt.

Zahnhygiene während der Therapie mit Denosumab (Xgeva®)
Eine gründliche Zahnhygiene ist während der Therapie unerlässlich. Sie sollten folgende Dinge berücksichtigen:

- Benutzen Sie am besten eine mittelstarke Zahnbürste.

- Blutende Stellen sollten besonders gut gereinigt werden. Gehen Sie insgesamt behutsam vor.

- Bürsten Sie Ihre Zähne und Zunge nach jeder Mahlzeit und vor dem Zubettgehen.

- Reinigen Sie Ihre Zahnzwischenräume einmal am Tag vorsichtig mit Zahnseide und/oder einem Spezialbürstchen (Apotheke, Zahnarzt), um Zahnbelag (Plaque) auch an diesen Stellen zu entfernen

- Einige Medikamente verursachen als Nebenwirkung „Mundtrockenheit“. Zahnverfall und andere Zahnprobleme können die Folge sein. Wenn Sie Ihren Mund mehrmals täglich mit Wasser spülen und die Speichelbildung z.B. durch das Kauen von zuckerfreiem Kaugummi anregen, können Sie einem trockenen Mund wirksam entgegenwirken.

- Verwenden Sie kein alkoholhaltiges Mundwasser.

Kontrollieren Sie täglich mit Hilfe eines Spiegels Ihre Zähne und Ihr Zahnfleisch auf z.B. wunde Stellen oder Zahnfleischbluten. Wenn Sie Veränderungen bemerken oder Schmerzen im Mund, an den Zähnen oder im Kiefer haben, berichten Sie dies umgehend an Ihren Zahnarzt oder Onkologen/Prüfarzt.

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DETECT III

Übersicht der Untersuchungen - Studienablauf für Patientinnen

Visiten	Screeningbesuch max. 21 Tage vor Randomisationsbesuch	Randomisationsbesuch max. 21 Tage nach Screening-Besuch	Kontrollbesuche alle 3 oder 4 Wochen	Abschlussbesuch 12 Monate nach Therapiebeginn oder bei vorzeitigem Therapieabbruch	Follow-Up-Besuche 2-4 Wochen nach Abschlussbesuch, dann alle 3 Monate
Gespräch mit Prüfarzt (Anamnese) (Dauer ca. 30 Minuten)	X				
Unterschrift der Einwilligungs- und Datenschutzerklärung Teil 1	X				
Blutentnahme (zum Nachweis von verstreuten Tumorzellen im Blut, die HER2/neu aufweisen) (Dauer ca. 10 Minuten)	X		X (alle 8-12 Wochen)		
Gespräch mit Prüfarzt (ausführliche Anamnese) (Dauer ca. 30 Minuten)		X			
Unterschrift der Einwilligungs- und Datenschutzerklärung Teil 2		X			
Ggf. Unterschrift der Einwilligungs- und Datenschutzerklärung Teil 3		X			
Körperliche Untersuchung (inkl. Messung von Blutdruck, Puls, Körpertemperatur, Größe und Gewicht (Dauer ca. 20 Minuten)		X	X	X	
Blutentnahme (Routine-Laborwerte + Tumormarker ggf. + Abnahme weiterer ca. 50 ml Blut für Forschungszwecke) (Dauer ca. 10 Minuten)		X	X Tumormarker: bei jeder Tumorbeurteilung (ca. alle 8-12 Wochen)	X	
Schwangerschaftstest (Urinprobe oder Blutentnahme)		X			

DETECT III

Visiten	Screeningbesuch max. 21 Tage vor Randomisationsbesuch	Randomisationsbesuch max. 21 Tage nach Screening-Besuch	Kontrollbesuche alle 3 oder 4 Wochen	Abschlussbesuch 12 Monate nach Therapiebeginn oder bei vorzeitigem Therapieabbruch	Follow-Up-Besuche 2-4 Wochen nach Abschlussbesuch, dann alle 3 Monate
Beurteilung der Brustkrebserkrankung mittels bildgebenden Untersuchungen (z.B. CT, MRT, Röntgen und/oder Ultraschall) (Dauer abhängig von Art der Untersuchung jeweils ca. 15-60 Minuten)		X	X (alle 8-12 Wochen)		
Herzuntersuchung mit EKG und Ultraschall (Echokardiographie) (Dauer ca. 30 Minuten)		X		X (nur Echokardiographie)	
Befragung zur Lebensqualität anhand eines Fragebogens (Dauer ca. 15 Minuten)		X	X	X	
Dokumentation etwaiger Schmerzen auf einer Skala		X	X	X	
Erhebung unerwünschter Ereignisse		X	X	X	X
Dokumentation von Begleitmedikamenten		X	X	X	X
Ausgabe von Lapatinib-Tabletten + Zählung der Tabletten		(X)	(X)	(X)	