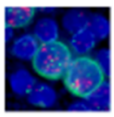
Version 2.1
09.04.2018



DETECT V / CHEVENDO

A multicenter, randomized phase III study to compare chemo- versus endocrine therapy in combination with dual HER2-targeted therapy of Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisqali® (ribociclib) in patients with HER2 positive and hormone-receptor positive metastatic breast cancer.

In cooperation with

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

EudraCT Number 2014-002249-22

ClinicalTrials.gov Identifier: NCT02344472

Sponsor:	**Universitätsklinikum Ulm (AöR)** **Albert-Einstein-Allee 29** **D-89081 Ulm**
Sponsor's Responsible Person:	**Prof. Dr. Wolfgang Janni** **Department of Obstetrics and Gynecology** **University Hospital Ulm** **Prittwitzstr. 43** **D-89075 Ulm**
Coordinating Investigator: („Leiter der klinischen Prüfung" according to §4 (25) German Drug Law)	**Prof. Dr. Jens Huober** **Department of Obstetrics and Gynecology** **University Hospital Ulm** **Prittwitzstr.43** **D-89075 Ulm**
Biomaterial Coordinating Lead Labaratory	**Frauenklinik der LMU - Campus Innenstadt** **Tumorimmunologisches Labor, Zi. 123** **Maistraße 11** **D-80337 München**

Clinical Study Protocol

ClinicalTrials.gov Identifier: **NCT 02344472**

EudraCT-No.: **2014-002249-22**

Title **Chemo- versus endocrine therapy in combination with dual HER2-targeted therapy of Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisqali® (ribociclib) in patients with HER2 positive and hormone-receptor positive metastatic breast cancer**

Short Title **DETECT V / CHEVENDO**

Protocol Version **Version 2.1**

Protocol Code No. **D-V**

Date of Protocol **09.04.2018**

Study Phase **Phase IIIa**

Sponsor in terms of §4 (24) AMG (German Drug Law)

Universitätsklinikum Ulm (AöR)
Albert-Einstein-Allee 29
D-89081 Ulm

Responsible person for the observance of the sponsor's trial-related duties and functions

Prof. Dr. Wolfgang Janni
University Hospital Ulm
Department of Obstetrics and Gynecology
Prittwitzstr.43
D-89075 Ulm
Germany
Phone: +49 (0) 731-500 58501
Fax: +49 (0) 731-500 58502
E-Mail: Wolfgang.Janni@uniklinik-ulm.de

National Coordinating Investigator ("Leiter der klinischen Prüfung" according to § 4 (25) German drug law)

Prof. Dr. Jens Huober
University Hospital Ulm
Department of Obstetrics and Gynecology

Prittwitzstr.43
D-89075 Ulm
Germany
Phone: +49 (0) 731-500 58501
Fax: +49 (0) 731-500 58502
E-Mail: Jens.Huober@uniklinik-ulm.de

Co-Directors:

Prof. Dr. D. Wallwiener, Tübingen
Prof. Dr. T. Fehm, Düsseldorf
Prof. Dr. H. Tesch, Frankfurt
Prof. Dr. A. Schneeweiß, Heidelberg
Prof. Dr. V. Müller, Hamburg

Clinical Research Organization

Alcedis GmbH
Winchesterstraße 3
D- 35394 Gießen
Germany
Phone: +49 (0)641-94436 0
Fax: +49 (0)641-94436 70

Boards and Committees

Protocol Board:

- Prof. Dr. Tanja Fehm, Düsseldorf
- Prof. Dr. Wolfgang Janni, Ulm
- Prof. Dr. Volkmar Müller, Hamburg
- Prof. Dr. Jens Huober, Ulm
- PD Dr. Brigitte Rack, München
- PD Dr. Thomas Friedl, Ulm
- Dr. S. Albrecht, Ulm
- Dr. A. De Gregorio, Ulm
- A. Polasik, Ulm
- T. Romashova, Ulm
- Prof. Dr. Hans Tesch, Frankfurt
- Prof. Dr. Diethelm Wallwiener, Tübingen
- Prof. Dr. Andreas Schneeweiß, Heidelberg

Data Safety Monitoring Board (DSMB):

- Prof. Dr. Harald Sommer, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Klinikum der Universität München, München
- Dr. Lothar Häberle, Universitätsfrauenklinik Erlangen, Erlangen
- Prof. N. Lynn Henry, Division of Hematology/Oncology, University of Michigan Comprehensive Cancer Center, University of Michigan, Michigan
- Prof. Dr. Matthias Schwab, Robert-Bosch-Krankenhaus, Institut für Klinische Pharmakologie, Stuttgart

Signature Sheet

Sponsor University Hospital Ulm

Sponsor's responsible person: Prof. Dr. Wolfgang Janni
University Hospital Ulm
Department of Obstetrics and Gynecology
Prittwitzstr.43
D-89075 Ulm

09.04.2018 _____
Date Signature

National Coordinating Investigator (LKP)

Prof. Dr. Jens Huober
University Hospital Ulm
Department of Obstetrics and Gynecology
Prittwitzstr.43
D-89075 Ulm

09.04.2018 _____
Date Signature

Statistical Processing PD Dr. rer. nat. Thomas Friedl
University Hospital Ulm
Department of Obstetrics and Gynecology
Prittwitzstr. 43
D-89075 Ulm

09.04.2018 _____
Date Signature

Clinical Research Organization Alcedis GmbH
Dr. Ina Santjer-Schnabel
Winchesterstraße 3
D- 35394 Gießen

09.04.2018 _____
Date Signature

Investigator Signature Page

Sponsor's Protocol Code Number

EudraCT-No	**2014-002249-22**
Title	Chemo- versus endocrine therapy in combination with dual HER2-targeted therapy of Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisqali® (ribociclib) in patients with HER2 positive and hormone-receptor positive metastatic breast cancer
Short Title	DETECT V / CHEVENDO
Protocol Version	**Version 2.1**
Date of Protocol	**09.04.2018**

I confirm that I have read this study protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the Declaration of Helsinki 1996 (Somerset West, Republic of South Africa), the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I am aware of my responsibilities as an Investigator/Representative under the GCP national regulations and trial protocol. I agree to appropriately direct and assist the staff under my control, who will be involved in this clinical trial. This is documented in a training log.

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.

Site Number: _____

Site Name: _____

Site Address: _____

_____

_____	_____	_____
Date	Investigator, Print Name	Signature

_____	_____	_____
Date	Representative, Print Name	Signature

SPONSOR'S STUDY OFFICE:

Universitätsfrauenklinik Ulm
Studienzentrale
Prittwitzstr. 43
D-89075 Ulm
Germany

Physicians: Dr. A. de Gregorio, T. Romashova, Dr. F. Schochter, A. Polasik, Prof. Dr. C. Scholz, Prof. Dr. J. Huober

Study Coordinators: Evelyn Ziel, Jessica D'Andrea, Heike Karl, Sabrina Krause

Phone: +49 (0) 731-500 58520
Fax: +49 (0) 731-500 58526
studienzentrale.ufk@uniklinik-ulm.de

CENTRAL LABORATORIES:

Biomaterial Coordinating Lead Laboratory:

Universitätsfrauenklinik Ulm
Endokrinologisch-onkologisches Labor (EOL)
Frauensteige 14, Haus 19
z. Hd. J. Kaufmann
D-89075 Ulm
Tel.: +49 (0) 731 500 58599
Fax: +49 (0) 731 500 58804
Email: julia.kaufmann@uniklinik-ulm.de

Forschungslabore der Frauenklinik
Life Science Center Düsseldorf
Merowingerplatz 1A
z. Hd. Dr. rer. nat. Dieter Niederacher
D-40225 Düsseldorf
Tel.: +49 (0) 211 385428 120
Fax: +49 (0) 211 385428 160
Email: Niederac@med.uni-duesseldorf.de

Universitätsklinikum Hamburg-Eppendorf
Institut für Tumorbiologie
Campus Forschung N27
z. Hd. Dr. Riethdorf/ C. Coith
Martinistraße 52
D-20246 Hamburg
Tel.: +49 (0) 407410 57497
Fax: +49 (0) 407410 55379
Email: tumorbiologie@uke.de

Universitätsfrauenklinik Tübingen
Labor für Tumorzelldissemination

z.Hd. Frau Ute Hilcher / Fach 166
Calwerstraße 7
D-72076 Tübingen
Tel.: +49 (0) 7071 29 86299
Fax: +49 (0) 7071 29 4947
Email: Ute.Hilcher@med.uni-tuebingen.de

List of Abbreviations Used in the Text

ABC	Advanced breast cancer
ADL	Activities of Daily Living
ADR	Adverse drug reaction
AE	Adverse event/experience
AESI	Adverse event of special interest
ALT	Alanine-aminotransferase (= SGPT = serum glutamate pyruvate transaminase)
AMG	*Arzneimittelgesetz* [German Medicinal Products Act]
ANC	absolute neutrophile cells
AST	aspartate-aminotransferase (= SGOT = serum glutamate oxalacetate transaminase)
AI	Aromatase inhibitor
AUC	Area under curve
BC	Breast cancer
CI	Confidence interval
CIN	Cervical Intraepithelial Neoplasia
CR	Complete response
CRF	Case report form
CRO	Clinical research organization
CT	Computer tomography
CTC	Circulating tumor cells
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Curriculum vitae
EC	Ethic committee
ECG	Electrocardiogram
eCRF	electronic case report form
e.g.	for example
ER	Estrogen receptor
FISH	Fluorescent In Situ Hybridization
5-FU	5-Fluorouracil
HER2	Human epidermal growth factor receptor 2
IB	Investigator's Brochure
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IRB	International Review Board
IRF	Independent Review Facility
ISF	Investigator site file
ITT	Intent to treat
IV	Intra venous
LP	last patient
LPI	Last patient in
MBC	Metastatic breast cancer
MRI	Magnetic resonance imaging
NSAI	Non-steroidal aromatase inhibitors
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PgR	Progesterone receptor
PD	Progressive disease
PFS	Progression free survival
PP	Per protocol
PR	Partial response

QAS	Quality-adjusted survival
QoL	Quality of life
RAID	Redundant Array of Independent Disks
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event/experience
SD	Stable disease
SmPC	*Produkt-/ Fachinformation* [Summary of medicinal Product Characteristics]
SSL	Secure Socket Layer
SUSAR	Serious unexpected severe adverse events
WBDC	Web Based Data Capture

Table of Contents

1 Synopsis

Study title	Chemo- versus endocrine therapy in combination with dual HER2-targeted therapy of Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisqali® (ribociclib) in patients with HER2 positive and hormone-receptor positive metastatic breast cancer
Protocol code number	D-V
Sponsor	University Hospital Ulm Responsible person: Prof. Dr. Wolfgang Janni University Hospital Ulm Department of Obstetrics and Gynecology Prittwitzstr.43 D-89075 Ulm
National Coordinating Investigator	Prof. Dr. Jens Huober University Hospital Ulm Department of Obstetrics and Gynecology Prittwitzstr.43 D-89075 Ulm
Study phase	Clinical phase IIIa
FDA “covered study”	☐yes ☒ no
Study sites	Up to 120 sites in Germany
Planned study period	Enrolment start date (FPI): Q3 / 2015 Enrolment finish date (LPI): Q2 / 2020 Treatment period end date (LP off treatment): Q2 / 2021 (Study treatment period: 12 months) Follow-up period end date (LP off study): Q2 / 2023 (Follow-up period: 24 months)
Study objectives	**Primary objective (before the amendment coming into effect):** The primary objective of this study is to assess the safety of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy in patients with HER2-positive, hormone-receptor positive metastatic breast cancer. Safety will be assessed by the proportion of patients experiencing any adverse event (as defined by the modified adverse event score) during the treatment period. The modified adverse event score includes all adverse events grade 3 or higher with the exception of neutropenia, which is only included if rated grade 4, and alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher.

	New primary objective: With the amendment coming into effect, the CDK4/6 inhibitor Kisquali® (ribociclib) is added to both therapy arms. Thus, the new primary objective of this study is to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisquali® (ribociclib) and standard endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy (followed by endocrine therapy plus ribociclib in combination with trastuzumab and pertuzumab as maintenance therapy) in patients with HER2-positive, hormone-receptor positive metastatic breast cancer. Tolerability will be assessed by the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period. The modified adverse event score includes all adverse events grade 3 or higher with the exception of neutropenia, which is only included if rated grade 4, and alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher. **Main secondary objectives:** The main secondary objectives of this study are • to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy for patients that were randomized before the amendment (i.e. the addition of ribociclib to both treatment arms) coming into effect. Tolerability will be assessed by the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period. • to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy for all patients that were randomized (irrespectively of whether they were randomized before or after the amendment – the addition of ribociclib to both treatment arms - coming into effect). Tolerability will be assessed by the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period. **Additional secondary objectives:**

	• to account for the addition of Kisquali® (ribociclib), the primary analysis will be repeated (as secondary explorative analysis) using a specific modified adverse event score for the ribociclib cohort that includes nausea, vomiting, diarrhea and stomatitis grade 2 (in addition to the adverse events included in the modified adverse event score as used for the primary analysis) • to assess quality-adjusted survival (as assessed by the Q-TWiST method) and to compare it between the two treatment arms • to compare efficacy between the two treatment arms as assessed by overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) based on local assessment according to RECIST v1.1 in each cohort. • to assess the incidence of CNS metastases, evaluated by contrast-enhanced computer tomography (CT) or, preferably, magnetic resonance imaging (MRI) according to RECIST v1.1 based on local assessment . • to assess additional aspects of quality of life based on the evaluation of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires • to determine presence and number of CTCs in the peripheral blood at baseline, 6 weeks after randomization, and after the 12-month study treatment period or at the time of progression, whatever comes first, and to assess the value of CTCs as indicator for therapy success • to determine the endocrine responsiveness score (ERS) of CTCs at baseline, 6 weeks after randomization, and after the 12-month study treatment period or at the time of progression, whatever comes first, and to assess the value of the ERS as indicator for therapy success • to evaluate and compare toxicity of both treatment arms • to evaluate the safety of the study treatments (all grades, all events) All additional secondary objectives that include comparisons between the two treatment arms will be performed using three different patient cohorts: - patients that received ribociclib (i.e., patients randomized after the amendment coming into effect) - patients that did not receive ribociclib (i.e., patients randomized before the amendment coming into effect) - the whole patient population

Study design	This is a prospective, open, multicentre, randomized phase IIIa clinical trial.
Planned number of patients	Total number of patients: 270
Subject selection	**Inclusion Criteria:** Patients will be **included** in the study only if they meet **all** the following criteria: • Signed, written informed consent in study participation • The primary tumor and/or biopsies from metastatic sites or locoregional recurrences have been confirmed as HER2-positive (FISH-positive or IHC 3+) and hormone receptor positive breast cancer by histopathology according to local testing • Metastatic breast cancer or locally advanced BC, which cannot be treated by surgery or radiotherapy only • **Pre- and postmenopausal women are allowed** • No more than two prior chemotherapies for metastatic disease • No more than two prior anti-HER2 therapies for metastatic disease • Pertuzumab retreatment is allowed if prior pertuzumab treatment was finished 12 months before • At least one measurable lesion assessable using standard techniques by Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v1.1) • Tumor evaluation according to RECIST version 1.1 has been performed within 4 weeks before randomization based on local assessment • Age ≥ 18 years • Standard 12-lead ECG values assessed by the local laboratory: - QTcF interval at screening < 450 msec (using Fridericia's correction) - Resting heart rate 50-90 bpm • Left ventricular cardiac ejection fraction (LVEF) ≥ 50% at baseline (as measured by echocardiogram) • ECOG Score ≤ 2 • Adequate organ function within 14 days before randomization, evidenced by the following laboratory results below: - absolute neutrophil count ≥ 1500 cells/µL, - platelet count ≥ 100000 cells/µL, - hemoglobin ≥ 9 g/dL, - ALT (SGPT) ≤ 2.0 × ULN (≤ 3.0 × ULN in case of liver metastases) - AST (SGOT) ≤ 2.0 × ULN (≤ 3.0 × ULN in case of liver metastases) - bilirubin ≤ 1.5 × ULN (with the exception of Gilbert's syndrome)

	- creatinine ≤ 2.0 mg/dl or 177µmol/L INR ≤ 1,5 • Patients must have the following laboratory values within normal limits or corrected to within normal limits with supplemets before the first dose of study medication: -Sodium -Potassium -Total calcium • In case of patients of child bearing potential: Negative serum pregnancy test at baseline (within 7 days prior to randomization) and agreement to remain abstinent (if it is in line with the preferred and usual lifestyle) or use single or combined non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of study treatment **Exclusion Criteria:** Patients will be **excluded** from the study for **any** of the following reasons: • History of hypersensitivity reactions attributed to trastuzumab, pertuzumab, ribociclib or to other components of drug formulation • Mandatory need for cytostatic treatment at time of study entry based on clinical judgment and national/international treatment guidelines • Known CNS metastases • Any concurrent severe, uncontrolled systemic disease, social or psychiatric condition that might interfere with the planned treatment and with the patient's adherence to the protocol • Progression on prior Pertuzumab therapy • Treatment with Pertuzumab within the last 12 months • Prior treatment with any mTOR- or CDK4/6-inhibitor • Treatment with any other investigational agents during trial • Known hypersensitivity to lecithin (soya) or peanuts • Life expectancy < 6 months • Patients with pre-existing grade ≥2 peripheral neuropathy are excluded from taxane-based chemotherapy • History of serious cardiac disease, including but not confined to: - history of documented heart failure or systolic dysfunction (LVEF < 50%) - high-risk uncontrolled arrhythmias i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia (ventricular

	tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block) - angina pectoris requiring anti-anginal medication - clinically significant valvular heart disease - evidence of transmural infarction on ECG - poorly controlled hypertension (e.g., systolic >180 mm Hg or diastolic >100 mm Hg) - any other cardiac condition, which in the opinion of the treating physician would make this protocol unreasonably hazardous for the patient • Dyspnea at rest or other diseases that require continuous oxygen therapy • Patients with poorly controlled diabetes or with evidence of clinically significant diabetic vascular complications • Patients with known infection with HIV, hepatitis B virus, or hepatitis C virus • Male patients • Pregnant, lactating or women of childbearing potential without a negative pregnancy test (serum) within 7 days prior to randomization, irrespective of the method of contraception used • Medical or psychological conditions that would not permit the subject to complete the study or sign informed consent • Participation in another clinical study within the 30 days before registration • Legal incapacity or limited legal capacity

Treatment schedules

General:

Patients will be treated with Herceptin® (Trastuzumab)/ Perjeta® (Pertuzumab) and chemotherapy or endocrine therapy (plus Kisqali® (ribociclib) after the amendment comes into effect only for newly enrolled patients) according to randomization. A switch from combination chemotherapy to endocrine based therapy or vice versa is not allowed. Patients in the chemotherapy arm will get maintenance endocrine therapy in combination with Herceptin® / Perjeta® (plus Kisqali® after the amendment comes into effect) after completing chemotherapy. Herceptin® (Trastuzumab)/ Perjeta® (Pertuzumab) have to be administered as intravenous infusions prior to chemotherapy.

Recommended dosing Perjeta® (Pertuzumab):
Initial dosing: 840 mg Perjeta® as intravenous infusion over 60 minutes, d1; for subsequent infusions: 420 mg Perjeta® as intravenous infusion over 30-60 minutes, q3w.

Recommended dosing Herceptin® (Trastuzumab):
Initial dosing: 8 mg/kg body weight Herceptin® as intravenous infusion over 60-90 minutes, d1; for subsequent infusions: 6 mg/kg body weight Herceptin® as intravenous infusion over 30 minutes, q3w.

Recommended dosing Kisqali® (ribociclib):

Ribociclib capsules (3 x 200 mg) will be taken orally per day (3-weeks-on/1-week-off schedule) in combination with standard endocrine therapy (as defined below).

Recommended dosing for combination chemo- or endocrine therapy:

Chemotherapy	**Recommended Dosing**
Docetaxel	75 mg/m^2 i.v. d1 q3w
Paclitaxel	Two chemotherapy regimens are available: 90 mg/m^2 i.v. d1, 8, 15 q4w or 80 mg/m^2 i.v. d1, 8, 15, 22 q4w; duration of the treatment with paclitaxel is at the discretion of the investigator, at least 4 months or until disease progression or inacceptable toxicity
Capecitabine	2 x 1000 mg/m^2 p.o. d1-14 q3w; duration of the treatment with capecitabine is at the discretion of the investigator at least 4 months or until disease progression or inacceptable toxicity

Vinorelbine	30 mg/m^2 i.v..* d1+d8 q3w; duration of the treatment with vinorelbine is at the discretion of the investigator (at least 4 months or until disease progression or inacceptable toxicity)
Nab-Paclitaxel	125 mg/m² d1, 8, 15 q4w; duration of the treatment with nab-paclitaxel is at the discretion of the investigator (at least 4 months or until disease progression or inacceptable toxicity)
Eribulin	1,23 mg/m² i.v. d1, 8 q3w; duration of the treatment with eribulin is at the discretion of the investigator (at least 4 months or until disease progression or inacceptable toxicity)
Endocrine therapy	**Recommended Dosing**
Exemestane	25 mg/d p.o.
Letrozole	2,5 mg/d p.o.
Anastrozole	1 mg/d p.o.
Fulvestrant	500 mg i.m. d1+15+28, then 500 mg i.m. q28d
Leuprorelin	3,75 mg 1 M Depot s.c. q4w, 11,25 mg 3 M Depot s.c.
Goserelin	3,6 mg s.c. q4w

	Duration of study treatment: • depends on the agents and dose regimes chosen • depends on the occurrence of tumor progression, inacceptable toxicity or other criteria for discontinuation • Duration of chemotherapy should not be less than 4 months (unless earlier treatment discontinuation is medically indicated). Up to three weeks after completion of chemotherapy, patients will be treated with maintenance endocrine therapy, After max. 6 weeks following completing of chemotherapy maintenance therapy with ribociclib in combination with standard endocrine therapy must be started. • is limited to the 12 month study treatment period, but all therapies can be extended beyond the end of the study treatment period if medically indicated *Treatment in Follow-up Period:* Therapy after the study treatment period (i.e. treatment in the follow-up period) is at the discretion of the investigator. All therapies given in the study treatment period can be extended if medically indicated; study medication will be provided until the end of the follow-up period.
Statistical hypothesis	**Study Populations** *Intention to Treat (ITT) Set:* All randomized patients will be included in the ITT population. *Tolerability Set:* All randomized patients who received at least one dose of the study treatment and have at least one post-baseline safety assessment (the statement that a patient had no adverse events on the Adverse Event CRF is also regarded as a safety assessment). Patients who do not receive any amount of study medication will be excluded from the tolerability population. *Per Protocol (PP) Set:* All patients of the ITT set who did not violate any inclusion or exclusion criteria and who were treated according to protocol. If necessary, modified or additional analysis sets may be specified in a Statistical Analysis Plan (SAP) prior to data base lock. **Statistical Methods** Statistical analysis of experimental data will be performed at the end of the studies. In the primary confirmatory analysis, the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period (i.e. the relative risk) will be compared between the two treatment arms using the χ^2 test, and both relative risk

	ratio and the corresponding 95% confidence interval will be reported. In addition, pre-specified explorative subgroup analyses will be conducted to compare the proportion of patients experiencing any adverse event (as defined by the modified adverse event score) during the treatment period between the two treatment arms in the prospectively defined subgroups (according to the stratification factors) of patients with and without visceral metastases, of patients in the first line and in higher lines of chemotherapy treatment, and of patients with and without previous therapy with trastuzumab. The primary confirmatory analysis will be performed for all patients randomized after the amendment (i.e., the addition of ribociclib in both treatment arms) comes into effect (see study objectives). According to the two main secondary study objectives stated above (see study objectives), this analysis will also be performed for the subset of patients randomized before the amendment coming into effect (i.e., all patients that did not receive ribociclib as part of the study treatment) and with the full tolerability and/or ITT set of patients (i.e., all patients randomized for this study). All analyses regarding the additional secondary objectives will have exploratory character only and will be performed using the following three different patient cohorts: - patients that received ribociclib (i.e., patients randomized after the amendment coming into effect) - patients that did not receive ribociclib (i.e., patients randomized before the amendment coming into effect) - the whole patient population The secondary endpoint quality-adjusted survival (QAS) will be analyzed using the quality-adjusted time without symptoms and toxicity (Q-TWiST) analysis method (see Goldhirsch et al. 1989; Glasziou et al. 1990; Gelber et al. 1993). All secondary endpoints and other outcomes that are calculated based on frequencies/rates (ORR, DCR, CR, PR, SD) will be summarized using frequency tables presenting absolute and relative frequencies together with appropriate confidence intervals. Comparisons between groups will be performed using suitable non-parametric statistical tests such as Fisher's exact test, χ^2-test, or Cochran-Mantel-Haenszel test. Progression-free and overall survival will be estimated by the Kaplan Meier product limit method, and median values, 95% confidence intervals and survival plots will be provided. When appropriate, progression-free and overall survival will be compared between groups using the logrank test, and additional multivariate analyses may be performed by

	suitable regression models (proportional hazard regression model, logistic regression). The presence and number of circulating tumor cells (CTCs) measured at different time points will be evaluated in a descriptive way. The temporal changes in the number of CTCs will be described and analysed using appropriate generalized linear mixed models. In addition, different measures of CTC dynamics (based on various threshold values, relative or absolute changes in CTC counts) and their value for evaluating therapy efficacy or as a prognostic tool will be examined in detail by explorative data analyses. More details regarding the statistical analyses will be provided in a Statistical Analysis Plan (SAP) which will be finalized prior to data base lock. Unless otherwise noted, all statistical calculations will be implemented using the SPSS system (IBM Cooperation, New York, USA). **Sample Size Assumptions** The study is designed as a two-arm parallel phase III randomized superiority trial. The main primary objective is to analyse (using the χ^2-test) whether the proportion of patients that are affected by adverse events as defined by the modified adverse event score (assessed based on NCI CTCAE Version 4.03) differs between the dual HER2-targeted plus endocrine-based treatment arm and the dual HER2-targeted plus chemotherapy treatment arm. The sample size calculations are based on the assumption that the probability of having an adverse event as defined by the modified adverse event score for patients with HER2 positive metastatic breast cancer treated with dual HER2-targeted plus chemotherapy is 86.3% (based on results of the CLEOPATRA trial; data provided by Roche). Based on this assumption, a minimum of 121 patients per treatment arm is required to detect a 20% decreased risk of having an adverse event as defined by the modified adverse event score (i.e. a relative risk ratio of 0.8) for patients treated with dual HER2-targeted plus endocrine therapy as compared to patients treated with dual HER2-targeted plus chemotherapy (90% power, two-sided test, $\alpha = 0.05$). Assuming a loss to follow-up rate of about 10%, 270 patients with HER2 positive and hormone-receptor positive metastatic breast cancer have to be recruited for this study. Due to the amendment with the addition of ribociclib to both randomization arms, a separate sample size calculation was performed to assess the statistical power for the new primary analysis for the ribociclib cohort. It is assumed that 90 patients will be recruited before the amendment comes into effect (i.e. these patients do not receive ribociclib). Accordingly, 180 patients will receive

	ribociclib. Based on the assumption that the probability of having an adverse event as defined by the modified adverse event score for patients with HER2 positive metastatic breast cancer treated with dual HER2-targeted plus chemotherapy is 86.3% (see above), a sample size of 80 patients per treatment arm (180 patients receiving ribociclib, about 10% loss to follow-up assumed) will result in 76% power (two-sided test, $\alpha = 0.05$) to detect a 20% decreased risk of having an adverse event as defined by the modified adverse event score (i.e. a relative risk ratio of 0.8) for patients treated with dual HER2-targeted plus ribociclib and standard endocrine therapy as compared to patients treated with dual HER2-targeted plus chemotherapy followed by endocrine therapy plus ribociclib in combination with trastuzumab and pertuzumab as maintenance therapy.

Schedule of visits and assessments

Visits	**Screening** Before randomization ([a] ≤ 28 d / [b] ≤ 14 d)	**Therapy visit** (Every 3 weeks)	**Week 6**	**Every 9 weeks** Week 9, 18, 27, 36, …	**End of therapy** 28 days after date of last study medication	**FU** Every 3 months for 2 years
Written informed consent	X[a]					
Inclusion-/Exclusion criteria	X[a]					
HER2-status[1]	X[a]					
Hormone receptor status[2]	X[a]					
Anamnesis	X[a]					
Size[3], weight	X[a]	X				
Vital parameter[4]	X[a]	X			X	
Physical examinations	X[a]	X			X	
Previous and concomitant medication	X[a]	X			X	
ECOG/ Karnofsky-Index	X[a]	X			X	X
Differential blood count[5]	X[b]	X			X	
Biochemistry[6]	X[b]	X[12]			X	
Coagulation	X[b]					
Urine stick	X[b]					
Pregnancy test (for pre-menopausal females)[7]	X[b]			X	X	X
Tumor assessment (CT thorax / abdomen)[8]	X[a]			X	X	
12-channel-ECG[9]	X[a]	X[12]				
ECHO / LVEF	X[a]			X		
Administration of Herceptin® (trastuzumab)		X				
Administration of Perjeta® (pertuzumab)		X				
Administration of chemotherapy / hormones		X				
Adverse events[10]		X	X		X	X
Quality of life (EORTC-QLQ C 30 + BR23)	X[a]			X	X	X
Blood sampling for CTC determination analysis[11]	X[a]		X		X[11]	
Survival						X

[1)] Of primary tumor or metastasis; HER2-positivity is defined as immunohistochemistry (IHC) score 3+ or fluorescent in situ hybridization (FISH) positive, whichever was performed.

[2)] Hormone receptor status is defined as positive in case of ≥ 1 % stained cells for estrogen and/or progesterone (IHC)

[3)] Only at screening

[4)] Puls, blood pressure, body temperature

[5)] Prior to randomization / administration of study medication: Hemoglobin, absolute neutrophil count, leucocytes, platelets

[6)] Bilirubin, Creatinine, AST, ALT

For all patients that are treated with ribociclib: sodium, potassium, calcium, phosphorous, GGT, AP, and LDH; at baseline and if clinically indicated: total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. Monitor electrolytes at the beginning of each cycle for 6 cycles, and as clinically indicated.

[7)] For women of childbearing potential, a serum β-HCG test must be performed within 7 days prior to randomization. During treatment period and within 7 months after last dose of pertuzumab, a urine pregnancy test must be performed every 9 weeks during targeted therapy (approximately every 3 cycles) and as clinically indicated. Any positive urine pregnancy test must be confirmed via a serum β-HCG test. Treatment period pregnancy test results must be available prior to drug infusion.

[8)] Please use for every assessment the same method; assessment according RECIST version 1.1

[9)] In case of anomalies more ECGs during therapy

[10] The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[11)] Only in patients who consent to participate in translational research. If a patient disagrees to blood sampling for this purpose, she may nevertheless participate in the study. Blood samples for CTC analyses will be collected at baseline (i.e. before the start of treatment), 6 weeks after randomization, and after the 12-month study treatment period or at the time of progression, whatever comes first.

[12)] Ribociclib treatment:
- ECG must be performed on d15 of cycle 1, d1 cycle 2, and as clinically indicated
- Liver Function Test (LFT)must be monitored every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

2 BACKGROUND INFORMATION AND STUDY RATIONALE

2.1 Breast cancer

With an estimated 1.67 million new breast cancer (BC) cases diagnosed in 2012 (25% of all cancers), breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women both in more and less developed regions. Incidence rates vary from 27 per 100,000 in Middle Africa and Eastern Asia to 96 in Western Europe. Breast cancer ranks as the fifth cause of death from cancer overall (522,000 deaths) and while it is the most frequent cause of cancer death in women in less developed regions (324,000 deaths, 14.3% of total), it is now the second cause of cancer death in more developed regions (198,000 deaths, 15.4%) after lung cancer. Due to higher survival rates in (high-incidence) developed regions, the range in mortality rates between world regions is less than that for incidence, with rates ranging from 6 per 100,000 in Eastern Asia to 20 per 100,000 in Western Africa (Source: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx; assessed 07.03.2014).
Despite significant improvements in early diagnosis and treatment of breast cancer, about 40% of women with breast cancer will relapse and ultimately die of metastatic disease. Recurrent or metastatic breast cancer (MBC) is an incurable malignancy with a median survival of about two years (Hortobagyi 1998). Treatment for MBC is palliative, and the goals are to reduce tumor size, to slow down progression and formation of new metastases, and to increase quality of life. Although initial treatments did not achieve these goals, in the last decade a number of studies using new agents have shown promising results with increased response rates and benefits both in terms of prolonged progression-free and overall survival and in terms of increased quality of life (Austreid et al. 2014).
The new approaches have become possible because it emerged in the last years that there is not one BC, but that different subtypes can be distinguished dependent on expression of certain hormone and growth factor receptors (Goldhirsch et al. 2013). Drugs directed against these molecules have been developed making a more individual therapy possible, in contrast to the traditional chemotherapy which attacks all rapidly dividing cells, irrespective of whether they are healthy or cancer cells.

2.1.1 Hormone-Receptor positive Breast Cancer

An important predictive and prognostic marker in breast cancer is the presence of estrogen receptor (ER) and/or progesterone receptor (PgR). Approximately 70% of all invasive breast cancers are positive for ER and/or PgR expressions at the time of diagnosis. Consequently, anti-estrogen therapies that antagonize ER functions (such as fulvestrant) or inhibit estrogen production (e.g. aromatase inhibitors [AIs]) have been extensively developed in oncology. Consequently, a number of AIs that reduce peripheral estrogen synthesis have been developed for the treatment of ABC. In postmenopausal women, aromatase inhibitors (AI) reduce peripheral estrogen synthesis by blocking the conversion of androgens to estrogens in non-ovarian tissues; synthesis in these tissues is the primary source of estrogens in postmenopausal women. AIs are generally used as the first line of therapy for women with HR+ breast cancer. The third generation AIs can be broadly classified into two groups: non-steroidal aromatase inhibitors (NSAI), mainly letrozole (Femara®) and anastrozole (Arimidex®) and steroidal aromatase inactivators, represented by exemestane (Aromasin®).

2.1.2 Cyclin D kinases in breast cancer

Cell cycle related genes and proteins are frequently deregulated in breast cancer. Approximately 15%-20% of human breast cancers exhibit amplification of the cyclin D1 (CCND1) gene while the majority of human mammary carcinomas overexpress CCND1 protein. Overexpression of CCND1 is seen early in breast cancer, and it is maintained at all

stages of breast cancer progression, including metastatic lesions and the continued presence of CDK4-associated kinase activity is actually required to maintain breast tumorigenesis.
Data from the Cancer Genome Atlas highlight the importance of the Cyclin/CDK/Rb pathway in luminal breast cancer (The Cancer Genome Atlas Network 2012). Abnormalities that result in CDK activation are highly enriched in the luminal A and B molecularly defined subgroups, approximately 85% of which were ER+/HER2-negative. Cyclin D1 amplifications were observed in 29% and 58% of the luminal A and B subtypes, respectively, and CDK4 amplifications were observed in 14% and 25% of luminal A and B subtypes, respectively. Luminal A subtype tumors also have loss of CDKN2C, which encodes p16INK4a, a CDK inhibitor. Although In preclinical models, pRb depletion appears to be associated with resistance to antiestrogen therapy, the luminal subtypes also maintain expression of Rb (The Cancer Genome Atlas Network 2012), which would be essential for benefit from treatment with a CDK4/6 inhibitor. Of note, the p16INK4a gene promoter is transcriptionally active in senescent, but not non-senescent cells. Furthermore, recent data exploring 47 human breast cancer cell lines demonstrated preferential sensitivity to CDK4/6 inhibitors in ER/HER2+ cell lines. Finally, recent preclinical data suggest that despite estrogen deprivation, ERα retains genomic activity and drives a CDK4/E2F dependent transcriptional program (Miller 2011).
Ibrance® (palbociclib) is a CDK4/6i, inhibitor indicated in combination with letrozole for the treatment of postmenopausal women with hormone receptor (ER)-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for metastatic disease (Ibrance Prescription Information). A randomized, open-label, multicenter study of palbociclib plus letrozole versus letrozole alone conducted in 165 postmenopausal women with ER-positive, HER2-negative advanced breast cancer with no previous systemic treatment for their disease showed a statistically significant improvement in PFS with the addition of palbociclib to letrozole (median PFS 20.2 months versus 10.2 months (HR 0.49; 95% CI:0.32 to 0.75; P=0.0004) (Finn 2014). This was confirmed in a randomized, multicenter, double-blind phase 3 study or palbociclib plus letrozole versus placebo plus letrozole in postmenopausal women who had not received any prior systemic anti-cancer treatment for advanced disease. The median PFS in this study was 24.8 months for the CDK4/6 inhibitor in combination with letrozole versus 14.5 months for placebo plus letrozole (HR=0.58 [0.46 to –0.72], P<0.000001). (Finn et al., Abstract 507, oral presentation at ASCO 2016, Chicago)
A phase III study in 521 patients with advanced HR+, HER2-negative advanced BC that had relapsed or progressed during prior endocrine therapy showed a median PFS of 9.2 months (95% CI, 7.5 to not estimable) with palbociclib in combination with fulvestrant vs 3.8 months (95% CI, 3.5 to 5.5) with placebo and fulvestrant (HR for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001) (Turner 2015). In this study, premenopausal and postmenopausal patients were enrolled and consistent benefit from palbociclib was seen in pre- and post-menopausal women. Pre- and peri-menopausal women also received goserelin in addition to the study medication.

2.1.3 HER2 positive Breast Cancer

The HER2 proto-oncogene encodes a transmembrane, receptor-like glycoprotein with intrinsic tyrosine kinase activity. Tyrosine kinase receptors are transmembrane receptors that bind extracellular ligands which – mediated by several phosphorylation steps – lead to the initiation and activation of signal transduction pathways (e.g., MAP Kinase and PI3 Kinase/AKT pathway) within the cell inducing cell growth, survival, and differentiation. These receptors are key regulators of normal cellular processes but also play a critical role in the development and progression of many types of cancer.
HER2 (human epidermal growth factor receptor 2, also known as c-erbB2 or neu) is a member of the epidermal growth factor receptor (EGFR/ERBB) family, a family of four structurally related receptor tyrosine kinases. Ligand binding results in dimerization, whereby homo- and hetero-dimerization of the EGFRs is possible (Hynes 1994).
Although 11 ligands are known to bind to various HER family members, none of these ligands binds directly to HER2. Instead, due to HER2 being the preferred dimerization partner it

functions as a co-receptor and is frequently activated by forming dimers with another HER family receptor, when activated in a HER ligand–dependent manner (Graus-Porta et al. 1997).
In approximately one-fifth of breast cancer tumors HER2 gene amplification can be detected involving overexpression and spontaneous receptor dimerization in the absence of a ligand and constitutive receptor activation. This process facilitates malignant tumorigenesis.
Overexpression of HER2 has been associated with certain particularly aggressive types of breast cancer that show increased disease recurrence and poor prognosis (Meric 2002) as well as resistance to chemotherapeutic and hormonal agents (Slamon et al. 2001).
HER2 over-expression 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).
In recent years HER2 has become an important biomarker and target of therapy.

2.1.4 Herceptin® (Trastuzumab)

Herceptin® is a recombinant humanized monoclonal antibody that binds specifically and with high affinity to the extracellular domain of HER2.
Proposed mechanisms of action include antibody-dependent cellular cytotoxicity, inhibition of intracellular signal transduction, inhibition of tumor angiogenesis, and inhibition of repair of DNA damage induced by concurrent chemotherapy (Spector et al. 2009).
Herceptin® has been shown to inhibit the proliferation of human tumor cells overexpressing HER2 both in vitro and in vivo. Its clinical efficacy and safety has been demonstrated in a series of Phase I, Phase II, and Phase III clinical trials in women with HER2-overexpressing MBC (Cobleigh et al. 1999, Slamon et al. 2001, Marty et al. 2005). As monotherapy and in combination therapy Herceptin® improved median survival and increased progression free survival (PFS) in a group of patients with previously poor outcome.

A prerequisite for Herceptin® therapy is the detection of HER2 protein overexpression (HER2-positive) because these are the only patients for whom benefit has been shown.
Herceptin® is indicated for the treatment of patients with MBC whose tumors overexpress the HER2 protein
- as monotherapy for the treatment of patients who have received one or more chemotherapy regimens for their metastatic disease,
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer,
- in combination with paclitaxel or docetaxel for the treatment of patients who have not received chemotherapy for their metastatic disease.
- in combination with lapatinib for the treatment of patients with hormone-receptor negative (HR-) metastatic disease that have progressed on prior trastuzumab therapy(ies) in combination with chemotherapy.

However, many patients with HER2-positive MBC eventually become resistant to Herceptin® therapy. Thus new therapy options are needed.

2.2 Investigational Medicinal Product: Perjeta® (Pertuzumab)

Perjeta® (pertuzumab) is the first in a new class of targeted cancer treatments called HER2 dimerization inhibitors.
It is a recombinant, humanized immunoglobulin monoclonal antibody, which targets the human epidermal growth factor receptor 2. By binding to the extracellular dimerization domain of HER2, it prevents dimerization with the other members of the HER family of receptors.
As a result ligand-initiated intracellular signaling through two major signal pathways, MAP kinase and PI3K, is inhibited, which can result in cell growth arrest and apoptosis, respectively (Agus et al. 2005).

Since Perjeta® and Herceptin® bind to distinct epitopes on the HER2 receptor without competing with each other, and have complementary mechanisms for disrupting HER2 signaling it seems obvious to combine both drugs in therapy.
Augmented anti-proliferative activity is seen in vitro and in vivo when Perjeta® and Herceptin® are given in combination.

2.2.1 Non-clinical Studies – Pharmacology, Pharmacokinetics, and Toxicology

In vitro, pertuzumab blocks heregulin (HRG)-induced activation of the phosphatidylinositol-3-kinase (PI3K) cell survival pathway, whereas trastuzumab does not do so effectively, suggesting that pertuzumab is superior to trastuzumab in blocking ligand-activated HER2 signaling (Nahta et al. 2004). Pertuzumab mediates antibody-dependent cell-mediated cytotoxicity in cell-based assays with the same potency as trastuzumab (Scheuer et al. 2009). In tumor xenograft studies in mice, pertuzumab augmented the antitumor effect of various cytotoxic drugs representing different mechanisms of action as well as other HER pathway inhibitors such as the HER1-targeting agent erlotinib.
Consistent with its IgG1 framework, pertuzumab has a long terminal half-life in mice, rats, and primates (approximately 10 days) following an initial rapid distribution phase (<1 day). In nude mice implanted with non-small cell lung cancer (NSCLC) tumors and breast cancer tumors > 80% suppression of tumor growth was seen after administering weekly doses (0.4–60 mg/kg) at steady-state trough concentrations of 5-25 µg/mL. Pertuzumab administered weekly by IV injection was generally well tolerated in primates at doses up to 150 mg/kg. Treatment-related diarrhea was noted at doses of 15 mg/kg and higher. More chronic dosing (> 12 weeks of weekly dosing) resulted in diarrhea related dehydration in monkeys. In vitro studies demonstrated that pertuzumab is compatible with human blood and does not cause hemolysis. Tissue binding of the antibody is consistent with reported distribution of HER2 expression. In an embryo-fetal development reproductive toxicity study, pertuzumab administered to pregnant cynomolgus monkeys, twice weekly, during the period of fetal organogenesis (gestation day 19 to 50), providing clinically relevant exposure levels, caused a dose-related increase in embryo-fetal abortion and death. In addition, low amniotic fluid volume (oligohydramnios) and microscopic evidence of delayed renal development (renal hypoplasia) were observed in all pertuzumab-treated groups. (Roche Investigator's Brochure Perjeta®, 13th Version, February 2014)

2.2.2 Non-clinical Studies – Combination studies of Perjeta® (Pertuzumab) with Herceptin® (Trastuzumab)

In vitro studies have shown synergistic activity of trastuzumab and pertuzumab when used in combination (Nahta et al. 2004). This combination therapy was then tested on two different HER2-positive human tumor xenograft models, KPL-4 (derived from metastatic breast cancer) and Calu-3 (derived from NSCLC) (Scheuer et al. 2009). The results clearly demonstrated that trastuzumab and pertuzumab have strong synergistic antitumor activity on both xenograft models, Calu-3 and KPL-4. Each antibody alone used at a fixed dose (30 mg/kg intraperitoneal loading dose, followed by 15 mg/kg/week maintenance dose for both drugs) was only able to slow down tumor growth, while the combination treatment (using the same dose as monotherapy) resulted in tumor regressions in both Calu-3 and KPL-4 xenograft models. Furthermore, trastuzumab and pertuzumab completely inhibited KPL-4 metastatic tumor spread in host animals. Moreover, addition of pertuzumab to trastuzumab therapy enhanced antitumor activity in KPL-4 xenograft tumors that had already progressed on trastuzumab single-agent treatment. (Roche Investigator's Brochure Herceptin®, 14th Version, October 2013)
The synergistic action of pertuzumab and trastuzumab may be explained by their complementary modes of action: while pertuzumab prevents the ligand-activated formation of HER2 heterodimers, trastuzumab can block the shedding of HER2 extracellular domain that would result in constitutively activated truncated receptors. Trastuzumab is thought to be

effective in disrupting ligand independent HER2-HER3-PI3K complexes, whilst pertuzumab prevents ligand-induced HER2-HER3 dimerization (Junttila et al. 2009).

2.3 Clinical Experience

2.3.1 Single-agent Studies with Perjeta® (Pertuzumab) and Herceptin® (Trastuzumab)

2.3.1.1 Pharmacokinetics

Similar pharmacokinetics have been observed across clinical studies, with no dose-dependent changes in clearance at doses ranging from 2.0 to 25.0 mg/kg (equivalent to 140 mg to 1750 mg for a 70 kg patient). Population pharmacokinetic analysis was conducted on all available pertuzumab concentration data obtained from 481 cancer patients across 12 Phase I/II/III studies, and clearance, central volume of distribution, and terminal elimination half-life were determined as 0.235 L/day, 3.11 L, and 18 days, respectively. Lean body weight and serum albumin were identified as statistically significant covariates for pertuzumab pharmacokinetics. Clearance decreased in patients with higher baseline albumin concentrations and increased in patients with greater lean body weight. However, sensitivity analyses indicated that dose-adjustment based on these covariates would not lead to a meaningful reduction in exposure variability since the covariate effect on pertuzumab exposure was relatively small compared to the overall inter-individual variability of the population.

No statistically significant effects of other covariates on PK parameters were detected, including demographic variables (age, gender, race) laboratory variables related to hepatic and renal function (ALT, AST, TBIL, ALK, CrCL), and disease variables (ECOG/KPS, MBC versus other tumor types, number of metastatic sites, liver metastases and concomitant chemotherapy).

The fixed (non-weight based) pertuzumab dosing regimen of an 840 mg loading dose followed by a 420 mg maintenance dose, administered q3w, is well supported by these population pharmacokinetic analysis results. Results from studies where pertuzumab was administered in combination with various small molecule chemotherapeutic agents (gemcitabine, capecitabine, erlotinib or docetaxel), indicate that pertuzumab does not alter the pharmacokinetics of these agents and the pharmacokinetics of pertuzumab is similar to that observed in single-agent pertuzumab studies. In addition, data from the Phase II study WO20697 (NEOSPHERE) and the Phase III study WO20698/TOC4129g (CLEOPATRA), demonstrated that there is no evidence of drugdrug interactions (DDI) between pertuzumab and trastuzumab, or between pertuzumab and docetaxel. Results from studies where trastuzumab was administered in combination with various antineoplasic therapeutic variables revealed no statistically significant effects on pharmacokinetic (PK) parameters or other covariates. Pharmocological data from two studies (BO15935, M77004) in HER2 positive metastatic breast cancer patients treated with trastuzumab+paclitaxel+doxorubicin revealed again no effect on pharmacokinetics by co-therapy with trastuzumab. A substudy (JP19959) evaluated data from patients with advanced stomach cancer treated with capecitabine and cisplatin with or without trastuzumab. Biological active metabolites of capecitabine were not influenced by a simultaneous therapy with cisplatin and trastuzumab. Results from the JP16003 study where trastuzumab was administered in combination with docetaxel indicate that trastuzumab does not alter the pharmacokinetics of these agents. Results of a direct comparison of trastuzumab-PK data evaluated within the M7704 study with trastuzumab-PK data of the H0648g study where trastuzumab was combinated with antrazykline + cyclophosphamide or paclitaxel indicated no significant effect on pharmacokinetics of trastuzumab. (Roche Investigator's Brochure Perjeta®, 13th Version, February 2014 and most current SmPC of Perjeta® and Herceptin®).

2.3.1.2 Efficacy

Low clinical activity has been observed in phase I/II studies conducted in patients with HER2 low-expressing tumors receiving single-agent pertuzumab: complete responses have not been

observed in any of these trials. In single-agent Phase II pertuzumab studies, partial responses or stable disease lasting ≥ 6 months have been observed in 15% of patients with ovarian cancer (Study TOC2689g; N=123) and in 8% of patients with HER2 low-expressing metastatic breast cancer (Study BO16934; N=78).

2.3.1.3 Safety

Five dose levels of pertuzumab ranging between 0.5 mg/kg and 15 mg/kg were evaluated in Study TOC2297g (N=21). The most commonly reported AEs were fatigue, vomiting, nausea, diarrhea and rash. The majority of AEs were NCI-CTCAE Grade 1 or 2 in severity. In a Japanese Phase I dose-escalation study, of pertuzumab doses up to 25 mg/kg (Study JO17076; N=18), the most common toxicities were diarrhea, rash, nausea, vomiting, and lymphopenia. The MTD was not reached in either study, and no clear dose-safety relationship was observed.

Safety data from five Phase II studies in various indications of pertuzumab monotherapy given at fixed (non-weight based) therapeutic doses showed that the most commonly reported AEs in patients receiving single-agent pertuzumab were diarrhea, fatigue nausea, vomiting and decreased appetite (> 20% of patients). The majority of these AEs were Grade 1 or 2 in severity. Hematological events, including leucopenia and neutropenia, occurred infrequently in patients treated with pertuzumab alone. The proportion of patients in the single-agent pertuzumab studies who experienced AEs that led to discontinuation from pertuzumab treatment was 7%. AEs leading to treatment discontinuation comprised a wide variety of events from different organ system classes. In total, 40% of patients receiving single-agent pertuzumab in Phase II studies (N = 386) experienced NCI-CTCAE Grade ≥ 3 AEs. Apart from gastrointestinal disorders, the incidence of Grade 3-4 events in the single-agent pertuzumab studies was < 10% in all SOCs. Diarrhea (6.5%) was the most commonly reported Grade 3-4 AE. Other AEs occurring in more than 2% of patients were vomiting, nausea, small intestine obstruction, dyspnea, pneumonia, pleural effusion, abdominal pain, constipation and fatigue.

A phase III PK/QTcF sub study within the CLEOPATRA trial determined whether pertuzumab affected the corrected QTcF interval or other electrocardiogram parameters after treatment with pertuzumab plus trastuzumab and docetaxel versus placebo plus trastuzumab plus docetaxel for first-line treatement of HER2-positive metastatic breast cancer. Thirty-seven female patients participated within this sub study trial. Both groups showed a normal QTcF range and were below critical thresholds on clinical relevance. Therefore, cardiac monitoring and concentration-QTcF modeling demonstrated that pertuzumab in combination with trastuzumab and docetaxel had no clinically relevant outcomes on QTcF prolongation (Garg et al. 2013). (Source: Roche Investigator's Brochure Perjeta®, 13th Version, February 2014).

For the most up to date safety information, please refer to the most current edition of the Investigator’s Brochure and the most current SmPC.

2.3.2 Combination studies of Perjeta® (Pertuzumab) with Herceptin® (Trastuzumab)

2.3.2.1 Efficacy

In the international, randomized, double-blind, phase III CLEOPATRA trial, the addition of pertuzumab to trastuzumab plus docetaxel was studied in patients with untreated HER2-positive locally recurrent, unresectable MBC (Baselga et al. 2012, Swain et al. 2013a).

For the patients with previously-untreated HER2-positive MBC, a statistically significant and clinically meaningful improvement in progression-free survival (PFS), based on tumor assessments by an independent review facility (IRF), was observed in patients treated with pertuzumab, trastuzumab and docetaxel (Ptz+T+D; N=402) compared with those receiving placebo, trastuzumab and docetaxel (Pla+T+D; N=406). PFS was prolonged at the median by 6.1 months and the risk of disease progression or death was reduced by 38% (Hazard ratio [HR] = 0.62; 95% CI = 0.51, 0.75; p < 0.0001) with an improvement in median PFS from 12.4 months to 18.5 months (see Figure 1). Results of the investigator-assessed PFS analysis (HR = 0.65 [0.54, 0.78], p < 0.0001; median 12.4 vs 18.5 months, respectively) were consistent with those observed for IRF-assessed PFS.

A higher percentage of patients receiving pertuzumab achieved an objective response (CR or PR), as assessed by the IRF (see Table 1) and, in those patients who achieved an IRF assessed objective response, the duration of response was longer in patients receiving pertuzumab compared with placebo (median 54.1 weeks Pla+T+D vs. 87.6 weeks Ptz+T+D). There was no evidence to suggest that the addition of pertuzumab to trastuzumab and docetaxel had a detrimental effect on patient-reported outcomes (HRQoL) based on the comparable time to symptom progression (assessed using the FACT-B questionnaire) between treatment arms (Cortés et al. 2013).

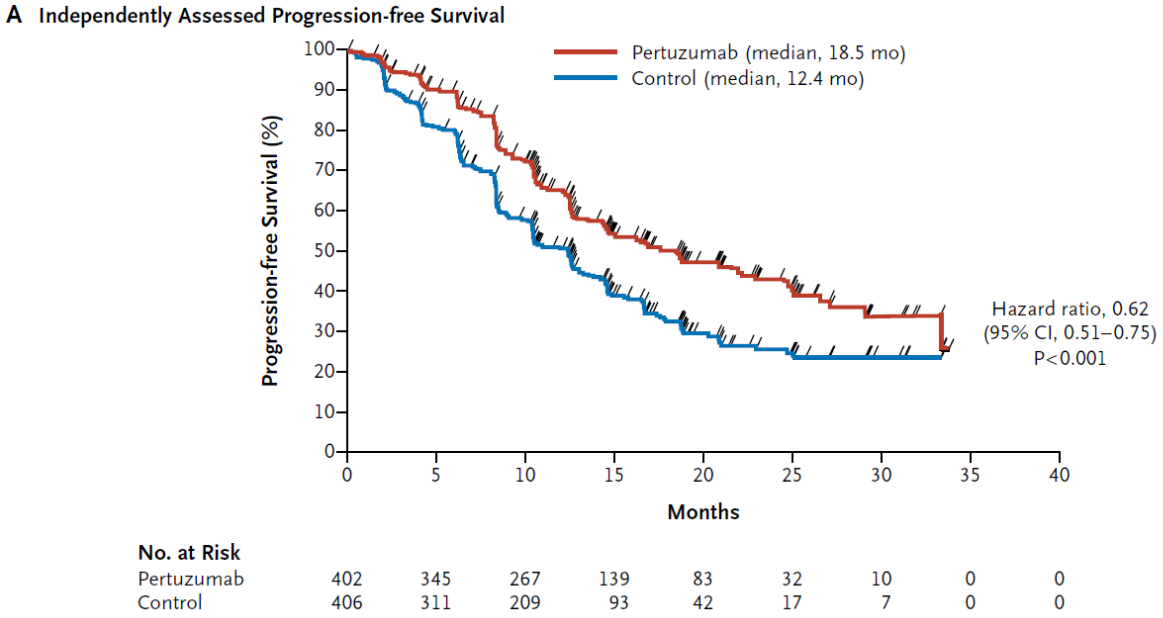


Figure 1: Kaplan-Meier estimates of progression-free survival as obtained in the CLEOPATRA-Study (Baselga et al. 2012)

Parameter	Pla+T+D N=406	Ptz+T+D N=402	HR (95% CI)	p-value
IRF-asessed PFS				
No. of patients with an event	242 (59.6%)	191 (47.5%)	0.62	< 0.0001
Median months	12.4	18.5	(0.51, 0.75)	
OS (first interim analysis)*:				
No. of patients who died	96 (23.6%)	69 (17.2%)	0.64 (0.47, 0.88)	0.0053[a]
OS (second interim analysis):				
No. of patients who died	154 (37.9%)	113 (28.1%)	0.66 (0.52, 0.84)	0.0008 [b]
ORR				
No. of patients analyzed	**336**	**343**		
Objective response (CR + PR)	233 (69.3%)	275 (80.2%)	Difference in ORR: 10.8% [4.2, 17.5]%	0.0011
Complete response (CR)	14 (4.2%)	19 (5.5%)		
Partial Response (PR)	219 (65.2%)	256 (74.6%)		
Median duration of response (months)	12.5	20.2		

[a] The HR and p-value for the first interim analysis of OS did not meet the pre-defined stopping boundary (HR ≤ 0.603, p ≤ 0.0012)

[b] The HR and p-value for the second interim analysis of OS met the pre-defined stopping boundary (HR ≤ 0.739, p ≤ 0.0138)

CR = complete response; IRF = Independent Review Facility; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; HR = hazard ratio; CI = confidence interval

Table 1: Overview of efficacy data of the CLEOPATRA-Study (Roche Investigator's Brochure Perjeta®, 13th Version, February 2014)

A second interim analysis of overall survival (OS; performed one year after the primary analysis of efficacy) crossed the predefined stopping boundary for statistical significance (p ≤ 0.0138), demonstrating that treatment with Ptz+T+D significantly improved OS when compared with Pla+T+D (HR = 0.66; 95% CI: 0.52, 0.84; p = 0.0008; see Figure 2). The updated analysis of investigator-assessed PFS demonstrated that the PFS benefit observed at the primary analysis was maintained after an additional year of follow-up. The HR of 0.69 and the increase in median PFS of 6.3 months (from 12.4 months in the Pla+T+D to 18.7 months in the Ptz+T+D) were highly consistent with those from the first analysis of investigator-assessed PFS and consequently also with the primary IRF analysis (see Table 1).

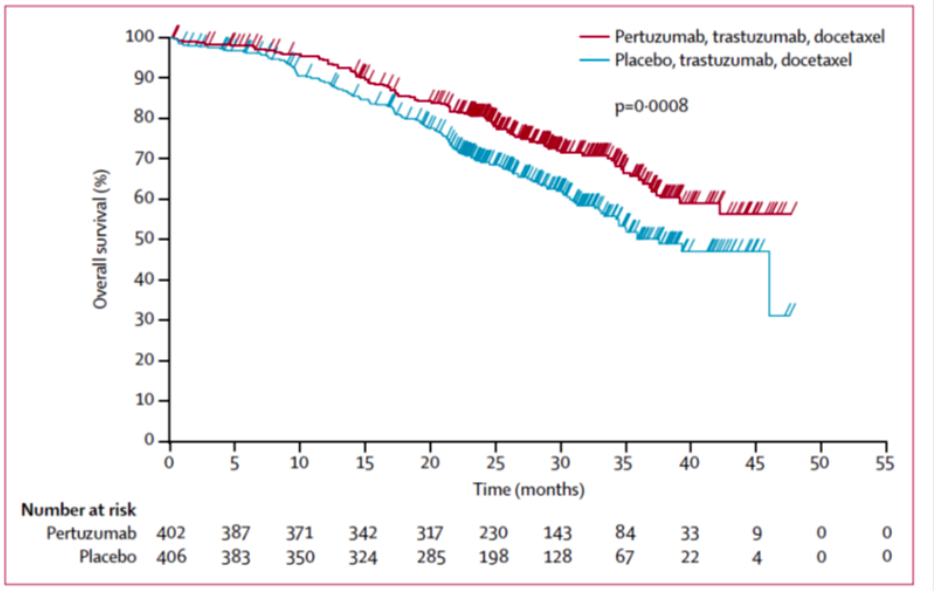


Figure 2: Kaplan-Meier estimates of overall survival as obtained in the CLEOPATRA-Study (Swain et al. 2013a)

PERTAIN is a multicenter, open-label, Phase II trial for post-menopausal women with HER2- and HR-positive breast cancer, studying the efficacy of the combination of pertuzumab plus trastuzumab with an aromatase inhibitor (AI) as first-line therapy for MBC.
Patients with HER2-positive, hormone receptor-positive LA/MBC who had not received prior systemic therapy (except endocrine therapy) were randomized 1:1 to Arm A: pertizumab in combination with Trastuzumab plus an AI or Arm B: Trastuzumab plus an AI. Patients may also receive induction chemotherapy (a taxane, either docetaxel or paclitaxel).
129 patients were randomized to Arm A and 129 to Arm B. Median PFS was 18.9 months in Arm A and 15.8 months in Arm B (HR 0.65; 95% CI 0.48–0.89; p=0.007). Median OS was not reached in either arm. ORR was 63.3% (95% CI 53.5–72.3) in Arm A and 55.7% in Arm B (95% CI 45.7–65.3; p=0.25). Median DoR was 27.1 months in Arm A and 15.1 months in Arm B (HR 0.57; 95% CI 0.36–0.91; p=0.02). All grade adverse events (AEs) occurred in 122 patients in each arm (96.1% in Arm A and 98.4% in Arm B); grade 3 AEs in 64 (50.4%) and 48 (38.7%) patients The most common grade 3 AEs (5%; Arm A vs. Arm B) were hypertension (10.2% vs. 11.3%), diarrhea (7.1% vs. 2.4%), and neutropenia (3.1% vs. 6.5%).

2.3.2.2 Safety

The evaluation of safety data obtained in the CLEOPATRA study (data cutoff 14 May 2012) showed that the overall safety profile, including the cardiac toxicity profile, of the pertuzumab combination regimen was generally comparable with that of the placebo-controlled arm (Table 2), apart from a higher incidence of Grade 1-2 diarrhea, rash, mucosal inflammation, dry skin and Grade 3-4 febrile neutropenia.
Overall, the most common AE by MedDRA PT was alopecia (61% in both arms), an AE associated with docetaxel (Table 2). Other frequently occurring AEs in both treatment arms were diarrhea, neutropenia, nausea, fatigue, rash, asthenia, decreased appetite, vomiting, peripheral edema, myalgia, and mucosal inflammation. The incidence of diarrhea, rash, mucosal inflammation, pruritus, febrile neutropenia and dry skin was higher (≥ 5% difference) in the Ptz+T+D arm than in the Pla+T+D arm. However, peripheral edema and constipation were more common (> 5% difference) in the placebo-controlled arm.
Although most AEs were Grade 1 or 2 in severity, the majority of patients experienced at least one Grade ≥ 3 AE (73.5% of patients receiving Pla+T+D vs. 76.2% of patients receiving Ptz+T+D). The majority of these AEs were blood and lymphatic system disorders (notably neutropenia). Grade ≥ 3 AEs of neutropenia (46% Pla+T+D vs. 49% Ptz+T+D), febrile

neutropenia (8% Pla+T+D vs. 14% Ptz+T+D) and diarrhea (5% Pla+T+D vs. 9% Ptz+T+D) were all more frequent (>2% difference) in patients receiving pertuzumab.
Blood and lymphatic system disorders were also the most frequently reported SAEs in both treatment arms. The incidence of SAEs was higher in the pertuzumab arm than in the placebo-controlled arm, primarily due to the greater number of reports of febrile neutropenia (14% of patients receiving the pertuzumab combination, compared to 8% of patients in the placebo-controlled arm).

AEs (%) by System Organ Class	Pla+T+D; N =397		Ptz+T+D; N=407	
	All Grades	Grades 3-4	All Grades	Grades 3-4
General disorders and administration site conditions				
Fatigue	37.4	3.3	38.0	2.2
Asthenia	30.6	1.8	27.0	2.5
Oedema peripheral	30.8	0.8	24.8	0.5
Mucosal inflammation	19.9	1.0	27.5	1.5
Pyrexia	18.2	0.5	19.1	1.2
Oedema	12.4	1.0	11.5	0.7
Skin and subcutaneous tissue disorders				
Alopecia	60.6	0.3	60.8	-
Rash	24.0	0.8	36.5	0.7
Nail disorder	23.2	0.3	23.0	1.2
Pruritus	10.1	-	16.7	-
Dry skin	5.8	-	10.8	-
Gastrointestinal disorders				
Diarrhoea	48.2	5.1	68.1	9.1
Nausea	42.4	0.5	43.9	1.2
Vomiting	24.5	1.5	25.5	1.5
Constipation	25.5	1.0	15.4	-
Stomatitis	15.7	0.3	19.9	0.5
Abdominal pain	12.4	0.8	15.0	-
Dyspepsia	12.1	-	13.2	-
Abdominal pain upper	10.6	-	10.3	0.2
Blood and lymphatic system disorders				
Neutropenia	49.7	46.0	52.9	49.0
Anaemia	19.4	3.5	23.5	2.5
Leukopenia	20.7	14.9	18.4	12.3
Febrile neutropenia*	7.6	7.6	13.7	13.7
Nervous system disorders				
Headache	18.9	0.8	23.8	1.5
Neuropathy peripheral	19.9	1.8	21.6	2.7
Dysgeusia	15.7	-	18.6	-
Dizziness	13.1	-	14.2	0.7
Peripheral sensory neuropathy	14.6	0.3	12.3	0.5
Paraesthesia	10.4	0.8	9.3	0.2
Musculoskeletal and connective tissue disorders				
Myalgia	24.5	0.8	23.8	1.2
Arthralgia	16.7	0.8	18.4	0.2
Pain in extremity	12.9	0.3	17.4	0.5
Back pain	11.9	1.0	15.0	1.5
Infections and infestations				
Upper respiratory tract infection	14.1	-	18.1	0.7
Nasopharyngitis	14.6	0.3	15.0	-
Respiratory, thoracic and mediastinal disorders				
Cough	19.7	0.3	23.0	0.5
Dyspnea	15.9	2.0	14.0	1.0
Metabolism and nutrition disorders				
Decreased appetite	26.5	1.5	29.7	1.7
Eye disorders				
Lacrimation increased	13.9	-	14.2	-
Vascular disorders				
Hypertension	8.1	1.8	10.5	2.0
Psychiatric disorders				
Insomnia	13.9	-	15.2	-

Table continues

AEs (%) by System Organ Class	Placebo+ trastuzumab + docetaxel; N =397		Pertuzumab+ trastuzumab + docetaxel; N=407	
	All Grades	Grades 3-4	All Grades	Grades 3-4

* denotes an AE term that has been reported in association with a fatal outcome

Table 2: Summary of common adverse events as observed in the CLEOPATRA study (Roche Investigator's Brochure Perjeta®, 13th Version, February 2014)

A total of 152 patients (38.4%) in the Pla+T+D arm and 113 patients (27.7%) in the Ptz+T+D arm had died at the time of the latest clinical cutoff. The most frequent cause of death in both treatment arms was PD; this was notably higher in the Pla+T+D arm (136 of 396 patients [34.3%]) compared with the Ptz+T+D arm (100 of 408 patients [24.5%]). When expressed as a percentage of total deaths, 89.5% of patients (136 of 152) in the Pla+T+D arm died of PD compared with 88.5% of patients (100 of 113) in the Ptz+T+D arm. Deaths due to causes other than PD were generally balanced between the two arms, and a similar number of patients died as a result of AEs (12 patients in the Pla+T+D arm vs. 8 patients in the Ptz+T+D arm; see Table 3). Febrile neutropenia or infections were the most frequent causes of death attributable to an adverse event (5 patients in the Pla+T+D arm and 5 patients in the Ptz+T+D arm).
At the time of the latest clinical cutoff, a similar proportion of patients in the two arms experienced AEs (regardless of causality) that led to discontinuation of all study treatments (6.1% in the Pla+T+D arm, 7.8% in the Ptz+T+D arm; Table 3). The most common reason for discontinuation (excluding events leading to discontinuation of docetaxel only) was left ventricular dysfunction (discontinuation of treatment for this reason was protocol mandated), followed by diarrhea.
AEs that led to discontinuation of docetaxel only were reported with a similar frequency in the two arms: 23.5% of patients in the Pla+T+D arm and 23.8% of patients in the Ptz+T+D arm. The most common AEs leading to discontinuation of docetaxel alone were general disorders and administration site conditions (in particular, edema), and nervous system disorders (in

particular, neuropathy peripheral). Seven patients in each treatment arm discontinued docetaxel as a result of neutropenia, and four patients in the pertuzumab arm discontinued docetaxel due to febrile neutropenia. The CLEOPATRA trial investigated negative effects of a combination therapy with trastzuzumab and pertuzumab. There have been no statistical significant differences between both study arms regarding most frequently reported cardiac AEs (QTcF prolongation, left ventricular dysfunction; Placebo+Trastzuzumb+Docetaxel:5/396 (1.26%), Pertuzumab+Trastuzumab+Docetaxel: 9/408 (2.21%); p=0.307).

Adverse Events	**Pla+T+D N = 396**	**Ptz+T+D N = 408**
Any AE	391 (98.7%)	408 (100%)
Related AEs	381 (96.2%)	397 (97.3%)
Grade 3 – 5 AEs	291 (73.5%)	311 (76.2%)
Serious AEs	115 (29.0%)	148 (36.3%)
AEs leading to		
• Discontinuation of any study medication [a]	114 (28.8%)	125 (30.6%)
• Discontinuation of all study medication	24 (6.1%)	32 (7.8%)
• Dose interruption / modification	215 (54.3%)	252 (61.8%)
AE resulting in death	12 (3.0%)	8 (2.0%)
Events to Monitor		
• Symptomatic LVSD assessed by the Investigator[b]	7 (1.8%)	5 (1.2%)
• Left ventricular dysfunction[c]	34 (8.6%)	22 (5.4%)
All Deaths	152 (38.4%)	113 (27.7%)

[a] includes discontinuation of docetaxel only

[b] Symptomatic LVSD (congestive heart failure, [CHF]) denotes patients experiencing a symptomatic decline in LVEF (NCI-CTCAE Grade ≥3) as measured by ECHO or MUGA. This was reported as an SAE under the PT "Left Ventricular Dysfunction

[c] Left ventricular dysfunction AEs identified by selecting the PT "Left Ventricular Dysfunction"

Table 3: Overview of adverse events data of the CLEOPATRA-Study (Roche Investigator's Brochure Perjeta®, 13th Version, February 2014)

Study MO22324 (PHEREXA) is an ongoing Phase III study of pertuzumab in combination with trastuzumab plus capecitabine versus trastuzumab plus capecitabine in the second-line metastatic setting in patients with HER2-positive MBC, who have progressed after trastuzumab-based therapy in the first-line metastatic setting. A safety review by the Independent Data Monitoring Committee (IDMC) held in April 2013 (275 patients enrolled) identified no new safety signals and recommended that the study continue. Furthermore, the IDMC recommended that the additional cardiac safety assessments that had been implemented as a precautionary measure in Protocol C (released in June 2010), were no longer required to be performed as there is no signal of added cardiotoxicity, at this time, over and above that which would be expected with a trastuzumab-chemotherapy combination. (Source: Roche Investigator's Brochure Perjeta®, 13th Version, February 2014)

Study MO27782 (VELVET) is an ongoing, two-cohort, open-label, multicenter Phase II trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab and vinorelbine in first line patients with HER2-positive advanced (metastatic or locally advanced) breast cancer. Patients in Cohort 1 receive pertuzumab and trastuzumab sequentially from separate infusion bags, followed by vinorelbine. Patients in Cohort 2 receive pertuzumab and

trastuzumab from a single infusion bag, followed by vinorelbine. An interim safety analysis was performed on data from Cohort 1 (N=106; clinical cutoff date: 10 September 2013):
At the time of the clinical cutoff, the most common AEs (≥ 20% of patients) in Cohort 1 were diarrhea, neutropenia, nausea, asthenia, fatigue, pyrexia, chills, vomiting, constipation, alopecia, and anemia. The most common AEs grade 3 or higher (in 3 or more patients) were neutropenia, leucopenia, diarrhea, febrile neutropenia, asthenia, constipation, anemia, bone pain, fatigue, hypersensitivity, and vomiting. Thirty patients (28.3%) experienced at least one SAE, with the most common event (in 2 or more patients) being febrile neutropenia, hypersensitivity, abdominal pain, drug hypersensitivity, and pyrexia. At the time of data cutoff, two patients had died due to an AE; one patient had a myocardial infarction and another had septic shock. Both events were considered to be unrelated to the study drug, by the investigator. Two patients discontinued study treatment due to an allergic or hypersensitivity reaction after receiving the first cycle of pertuzumab. One patient discontinued study treatment after the first cycle of pertuzumab and trastuzumab due to an adverse event (bronchospasm). During the course of study treatment, there was no overall decrease in mean LVEF from baseline. The proportion of patients with LVEF declines to <50% at Cycles 3, 6, 9, 12, and 15 was 1.1%, 2.5%, 2.8%, 3.8%, and 6.7%, respectively. (Source: Roche Investigator's Brochure Perjeta®, 13th Version, February 2014)

2.3.3 Investigational Medicinal Product: Kisqali® (Ribociclib)

In the mammalian cell cycle, entry into S phase is achieved by cyclin-dependet kinases 4 and 6 (CDK4/6). Ribociclib (formely LEE011) is an orally bioavailable, highly selective small molecule inhibitor of CDK4/6 that induces G1 arrest at sub-micromolar concentrations in a variety of retinoblastoma protein (pRB)-positive cancer cells in vitro. Ribociclib has proven efficacious when combined with other targeted therapies in vitro and in vivo in cancers driven by a variety of oncogenic signaling pathways. Ribociclib may therefore be an effective anti-cancer agent in a variety of pRb-positive human neoplasms, especially in those that contain an activated CDK4/6-pRb pathway. Ribociclib is currently being developed in phase III clinical trials for the treatment of hormone receptor positive (HR+) breast cancer patients; several other phase I or II clinical studies are being conducted and presented in the IB.

2.3.3.1 Experimental Nonclinical Data of Kisqali® (ribociclib)

A panel of human breast cancer cell lines was treated with increasing doses of ribociclib and dose-dependent inhibition of proliferation was observed across the panel with enhanced activity against ER+ breast cancer cell lines with IC50 < 1µM being observed for most ER+ breast cancer lines (Novartis internal data, ribociclib Investigator Brochure figure 4-3). Ribociclib as a single agent has been shown to have activity in preclinical models of ER+ breast cancer (Novartis internal data). In in vivo studies, combinations with the mTOR inhibitor RAD001 and PI3K inhibitor, BYL719, resulted in either improved or prolonged anti-tumor effects in tumor models derived from ER+ breast cancer.
In Jeko-1 MCL cells that overexpress cyclin D1 as a result of the t(11;14) chromosomal translocation, LEE011 inhibits the phosphorylation of pRb at CDK4/6-specific sites with an average IC50 of 60 nM. In nude rats bearing Jeko-1 subcutaneous xenografts, ribociclib demonstrates dose-dependent target inhibition in the tumors. LEE011 doses that induce >75% inhibition of pRb phosphorylation in this model are associated with complete tumor regression (see ribociclib Investigator Brochure Sections 4.1.1.2.1, 4.1.1.2.2). Ribociclib also inhibits the growth of many other tumor cell types in vitro and in vivo, including liposarcoma, melanoma, rhabdoid cancer, and carcinomas of the esophagus, breast, lung and pancreas. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti- tumor activity of ribociclib requires the presence of functional pRb. Refer to ribociclib Investigators Brochure for more details. Preclinical data generated using a primary model of ER+ breast cancer compared ribociclib at clinically relevant doses with the combination of ribociclib plus letrozole

(ribociclib Investigator Brochure Figure 4-10). Animals treated with the combination showed complete inhibition of tumor growth. Body weight was monitored throughout the treatment showing comparable results in all groups supporting the predicted lack of overlapping toxicity between ribociclib and letrozole.

The pharmacokinetics (PK) of ribociclib was investigated in mouse, rat, dog and monkey. Ribociclib showed high clearance (CL) in the mouse, rat, dog and monkey. The volume of distribution was large across species and the terminal elimination half-life (T1/2) was moderate in rodents and monkey (~2 to 5 h) and longer in dog (18 h). Bioavailability was low to moderate in rat (37%) and cynomolgus monkey (17%); moderate in mouse (65%) and dog (64%). Following oral administration, time to reach maximal plasma concentrations (Tmax) occurred between 2 to 4 h across species.
In a rat ADME (absorption, distribution, metabolism and excretion) study, extensive distribution of [3H]ribociclib and its metabolites was observed. In pigmented rats, radioactivity was specifically found in melanin-containing structures; the highest exposure to total radiolabeled components was observed in eye ciliary body, eye choroid, meninges, tactile hair and hair follicles. Radioactivity was not detected in the brain. Tlast (last observation timepoint) was ≤ 48h for most tissues, but long (168 to 840h) for lymph nodes, preputial gland, testis, eye and meninges. At one week ≤ 0.04% of the dose was retained in the carcass. LEQ803 (N-demethylation) was a prominent metabolite found in mouse, rat, dog, monkey and human hepatocytes. This metabolite retains some pharmacologic activity and interacts with human Ether-a-go-go Related Gene (hERG) channels in vitro. In male rats, unchanged ribociclib (24.7% of [3H]AUC0-24h) and its metabolite M11 (26.3% of [3H]AUC0-24h) were the major components in plasma.
In rats, ribociclib was eliminated mainly by metabolism with direct sulfation as the major pathway. Direct ribociclib secretion accounted for 18.2% of the total plasma clearance. In male dogs, metabolism was the major elimination route. The most prominent components in plasma were ribociclib (55.9% of [14C]AUC0-48h) and its metabolite LEQ803 (1.61% of [14C]AUC0-48h).
In vitro, ribociclib was a reversible inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4. Ribociclib may inhibit CYP3A4 under therapeutic conditions. No induction of CYP1A2, CYP2B6 or CYP3A4 was observed. Elimination of ribociclib is dominated by oxidative metabolism mainly via CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). The elimination of ribociclib may be affected by co-administered drugs that inhibit or induce CYP3A4.
Refer to ribociclib Investigators Brochure for more details.

2.3.3.2 Clinical experience with Kisqali® (ribociclib)

Ribociclib is currently being investigated in patients as a single agent in 3 phase I studies: (CLEE011X1101, CLEE011X2101, CLEE011X2102) in 2 phase II studies: (CLEE011X2201, CLEE011XUS03).
Ribociclib is being evaluated in several combination trials: letrozole (CLEE011A2201, CLEE011A2301, CLEE011A2115C), letrozole and alpelisib (CLEE011X2107), letrozole and buparlisib (CLEE011A2112C); goserelin, letrozole, anastrozole and tamoxifen (CLEE011E2301); fulvestrant (CLEE011F2301), fulvestrant and buparlisib (CLEE011X2108), everolimus and exemestane (CLEE011X2106), ceritinib (CLEE011X2110C) LDK378 (CLEE011X2110C), HDM201 (CHDM201X2103C), LGX818 (CLEE011X2105, CLGX818X2102), LGX818, MEK162 (binimetinib) buparlisib or LGX818, binimetinib and INC280 or LGX818, binimetinib and BGJ398 (CLGX818X2109) binimetinib (CMEK162X2114), or binimetinib and LGX818 (CMEK162X2110). These trials are ongoing with the exception of CLEE011A2201 and CLEE011A2112C where recruitment was prematurely terminated on 28-July-2014 and 20-Mar-2015 respectively. CLEE011A2301, CLEE011X2102 and 35CLEE011X2105 have also closed enrolment. The results of the phase I combination of letrozole and LEE011 (CLEE011X2107) are detailed in Section 1.2.6. The phase III trial

CLEE011A2301, investigating the combination of letrozole and ribociclib, reached its primary endpoint prematurely at the preplanned interim analysis.
Ribociclib is also being investigated in 4 clinical pharmacology studies: CLEE011A2102, CLEE011A2103, CLEE011A2109 and CLEE0112116. Three clinical pharmacology studies in healthy subjects have been completed: CLEE011A2101, CLEE011A2106 and CLEE011A2111.
Refer to the ribociclib Investigator Brochure for additional details.

2.3.3.3 Clinical safety with Kisqali® (ribociclib) as single agent

The most frequently reported AEs (≥10%), regardless of grade, causality and ribociclib dose were: nausea (52.3%); fatigue (40.9%); diarrhea (37.1%); vomiting (35.6%); neutropenia (34.1%); anemia (32.6%); decreased appetite, thrombocytopenia (23.5% each); white blood cell count decrease (22.7%); leukopenia (22%); constipation (21.2%); dyspnea (20.5%); asthenia (19.7%); cough (18.2%); hyperglycemia (17.4%); headache, hypoalbuminemia (16.7% each); ECG QT prolonged (15.9%); abdominal pain, back pain, lymphocyte count decrease, pyrexia (15.2% each); AST increase, blood creatinine increased, dizziness, lymphopenia (14.4% each); peripheral edema (13.6%); neutrophil count decreased (12.9%); ALT increase, pain in extremity (12.1% each) and hypocalcemia (11.4%).
For either continuous or intermittent dosing, the onset of neutropenia (most frequently Grade 2) occurs by Day 15, reaching a nadir in the third or fourth week with recovery during the week of drug holiday for the three weeks on/one week off schedule. Some patients require additional time for recovery (7 to 14 days). QT changes become evident in the first cycle by Day 8 and later (once steady state is reached), are associated with the maximum drug levels between 1 to 8 h post-dose, and remain stable or improve in subsequent cycles.
As of 15-Jun-2015, asymptomatic Grade 2 QTcF prolongation was observed with increasing frequency when increasing the dose starting at 600 mg: ten patients (13.5%) in the 600 mg cohort, three patients (21%) in the 750 mg cohort, four patients (31%) in the 900 mg cohort, and two patients (67%) in the 1200 mg cohort. Four patients (5.4%) at 600 mg and two patients (15%) at 900 mg had asymptomatic QTcF prolongation that resulted in a QTcF interval of 500 ms or more. As compared to baseline value, QTcF prolongation was at least 30 msec in 2 patients (50%) at 250mg, 2 (40%) at 350 mg and 400 mg, 59 (79.7%) at 600 mg, 11 (78.6%) at 750 mg, 11 (85%) at 900 mg and 2 (67%) at 1200 mg; and at least 60 msec in 23%, 0%, 39% and 67% of patients at 600 mg, 750 mg, 900 mg and 1200 mg, respectively. One grade 1 atrioventricular block of first degree was reported as related to ribociclib given at the dose of 140 mg.
There have been no deaths related to study drug reported on study [CLEE011X2101].The following serious adverse events shown in Table 4 have been reported with a suspected causal relationship in study [CLEE011X2101] as of 6-Aug-2015. For a complete list of AEs, all grades and Grade 3/4 that are suspected to be related to ribociclib refer to the ribociclib Investigators Brochure.

Serious suspected adverse events which have occurred with ribociclib (single agent)	
System Organ Class Preferred Term	Preferred Term
Blood and lymphatic system disorders	Anaemia, Febrile neutropenia, Neutropenia, Thrombocytopenia
Gastrointestinal disorders	Diarrhoea, Nausea,*Pancreatitis*
General disorders and administration site conditions	Generalized oedema
Infections and infestations	Herpes simplex
Investigations	***Blood creatinine increased,*** *Electrocardiogram QT prolonged*

Events in *italic font* indicate those events which are newly included since the previous edition of the reference safety information.

Refer to ribociclib Investigators Brochure for more details.

Table 4: Serious adverse events with a suspected causal reltionship with ribociclib as a singel agent

2.3.3.4 Clinical efficacy with Kisqali® (ribociclib) as single agent

Preliminary anti-tumor activity of ribociclib from trial [CLEE011X2101] was assessed across all dose levels (50 mg – 1200 mg). Out of 114 evaluable subjects as of 24-Apr-2014, 3 partial responses were observed at the 600 mg dose level; one each in BRAF/NRAS wild type with CCND1 amplified melanoma, and head and neck acinar carcinoma with CDKN2A loss (both on the 3 weeks on/1 week off regimen), and ER+/HER2-, PIK3CA mutant, CCND1 amplified breast cancer (on the continuous daily dosing regimen). Stable disease (SD) was the best overall response in 41 (37%) patients. Enrollment in this study is completed. Stable disease ≥4 cycles and ≥6 cycles was observed in 26 (24%) and 17 (15%) patients, respectively. Six patients with SD ≥4 cycles received treatment for >1 year, of these 2 patients were on study for >2 years (Jeffrey R Infante ASCO 2014 abstract 2528).

2.3.3.5 Clinical pharmacokinetics and pharmacodynamics of Kisqali® (ribociclib)

As of 15-Jun-2015, preliminary PK data were available from approximately 143 patients from the first-inhuman (FIH) study [CLEE011X2101] across the dose range of 50 to 1200 mg. Following oral dosing, ribociclib was rapidly absorbed with median Tmax ranging from 1 to 4 hours. Ribociclib plasma exposure (Cmax and AUC0-24h) exhibited slightly over-proportional increases in exposure across the dose range tested. Steady-state was generally reached by Day 8 and the mean effective T1/2 based on accumulation ratio (i.e., T1/2,acc) ranged from 12.3 to 42.9. The mean accumulation ratio (Racc) calculated from AUC0-24h at steady-state and AUC0-24h after a single dose across the studied doses ranged from 1.35 to 3.11.

At the recommended dose for future development (600 mg), steady-state plasma Cmax (n=56) ranges from 606-6170 ng/mL (geometric mean = 1790 ng/mL or 4.1 µM), median Tmax (n=72) is 2.1 h, and AUC0-24h (n=53) ranges from 6770-90600 ng*h/mL (geometric mean = 23600 h*ng/mL). At this dose, inter-patient variability in Cmax and AUC is 62% and 66%, respectively, as assessed by geometric coefficient of variation (CV%). At the 600 mg dose level, LEQ803, an active metabolite of ribociclib, accounted for approximately 8% (geometric mean) of ribociclib AUC0-24h after single and multiple doses. Refer to the ribociclib [Investigators Brochure] for more details.

In the human ADME study [CLEE011A2102], a single oral dose of 600 mg [14C]LEE011 was administered to 6 healthy male subjects. The majority of the administered dose was excreted in feces (69.1%), with a minor amount excreted in urine (22.6%). Absorption was estimated to be approximately 58.8%. Ribociclib accounted for approximately 23% of the total radioactivity in plasma, based on AUCinf. Metabolites M1 (glucuronidation of M15), M4 (LEQ803, N-demethylation) and M13 (CCI284, N-hydroxylation) were the most abundant metabolites in plasma, representing an estimated 7.78%, 8.60% and 9.39% of total [14C]AUC0-48h, and 17.9%, 19.8% and 21.6% of ribociclib AUC0-48h, based on metabolite profiles.

A DDI study with ritonavir (a strong CYP3A4 inhibitor) and rifampicin (a strong CYP3A4 inducer) was conducted in 48 healthy subjects [CLEE011A2101]. Compared to ribociclib alone, ritonavir (100 mg bid for 14 days) increased ribociclib Cmax and AUCinf by 1.7-fold and 3.2-fold, respectively, following a single oral dose of 400 mg ribociclib. Cmax and AUClast decreased by 96% and 98%, respectively. In summary, these results demonstrated that concurrent use of strong CYP3A4 inhibitors or strong CYP3A4 inducers may increase or decrease ribociclib exposure, respectively, and should be avoided and an alternative concomitant medication with less potential for CYP3A inhibition should be considered. If coadministration of ribociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of ribociclib to 400 mg once daily.

Paired skin biopsies from 55 patients treated with LEE011 at doses ranging from 50 to 900 mg and paired tumor biopsies from 20 patients (16 patients at 600 mg, 2 patients at 900 mg, and 1 patient each at 70 and 750 mg) were assessed for changes in Ki67 and pRb levels. Preliminary results indicate the following: in skin biopsies, reductions in Ki67 from baseline

were observed across all dose levels with a more consistent trend from 400 mg onwards; in tumor biopsies, reductions in Ki67 from baseline were observed in 18/20 patients; however, limited samples and varied tumor types prevent conclusions about any dose-response relationship from being drawn. Changes in pRb were not significant or consistent in either skin or tumor samples, possibly due to varied tumor types.

2.3.3.6 Combination Kisqali® (ribociclib) plus letrozole

The combination of ribociclib (600 mg) and letrozole (2,5 mg) was evaluated in the placebo controlled phase III MonaLEEsa-2 study (Hortobagyi et al. 2016). The combined treatment has shown that the duration of progression-free survival was significantly longer in the ribociclib group than in the placebo group (hazard ratio, 0,56; 95% CI, 0,43 to 0,72; P=3,29 x 10-6 for superiority). The median duration of follow-up was 15.3 months. After 18 months, the progression-free survival rate was 63% (95% confidence interval [CI], 54,6 to 70,3) in the ribociclib group and 42,2% (95% CI, 34,8 to 49,5) in the placebo group. In patients with measurable disease at baseline, the overall response rate was 52,7% and 37,1%, respectively (P<0,001).

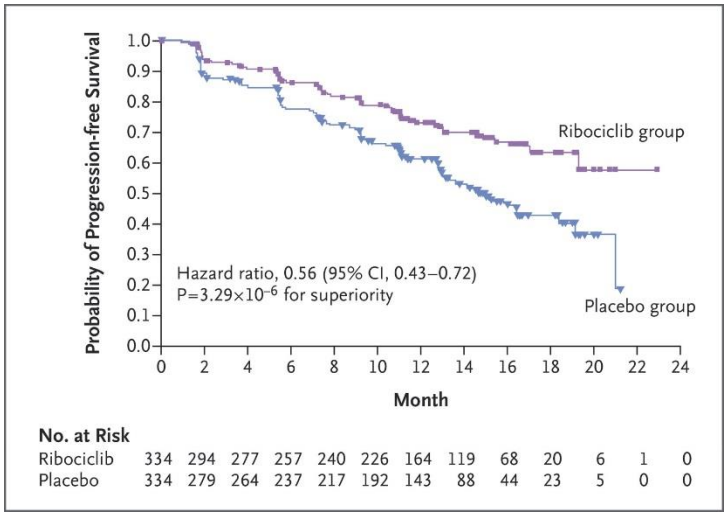


Figure 3: Kaplan-Meier Analysis of Progression-free Survival (Hortobagyi 2016)

In the safety population (334 patients in the ribociclib group and 330 in the placebo group), adverse events of any grade that occurred in at least 35% of the patients in either group were neutropenia (74,3% in the ribociclib group and 5,2% in the placebo group), nausea (51,5% and 28,5%, respectively), infections (50,3% and 42,4%), fatigue (36,5% and 30,0%, and diarrhea (35,0% and 22,1%) (Table 11). Nausea, infections, fatigue, and diarrhea were mostly grade 1 or 2. The most common grade 3 or 4 adverse events (≥5% of the patients in either group) were neutropenia (59,3% in the ribociclib group and 0,9% in the placebo group), leukopenia (21,0% and 0,6%, respectively), hypertension (9,9% and 10,9%), increased alanine aminotransferase level (9,3% and 1,2%), lymphopenia (6,9% and 0,9%), and increased aspartate aminotransferase level (5,7% and 1,2%). Febrile neutropenia occurred in 5 patients (1,5%) in the ribociclib group and in none in the placebo group.

Table 3. Adverse Events.*

Adverse Event	Ribociclib Group (N=334)			Placebo Group (N=330)†		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)
Neutropenia‡	248 (74.3)	166 (49.7)	32 (9.6)	17 (5.2)	3 (0.9)	0
Nausea	172 (51.5)	8 (2.4)	0	94 (28.5)	2 (0.6)	0
Infections	168 (50.3)	12 (3.6)	2 (0.6)	140 (42.4)	7 (2.1)	1 (0.3)
Fatigue	122 (36.5)	7 (2.1)	1 (0.3)	99 (30.0)	3 (0.9)	0
Diarrhea	117 (35.0)	4 (1.2)	0	73 (22.1)	3 (0.9)	0
Alopecia	111 (33.2)	NA	NA	51 (15.5)	NA	NA
Leukopenia	110 (32.9)	66 (19.8)	4 (1.2)	13 (3.9)	2 (0.6)	0
Vomiting	98 (29.3)	12 (3.6)	0	51 (15.5)	3 (0.9)	0
Arthralgia	91 (27.2)	2 (0.6)	1 (0.3)	95 (28.8)	3 (0.9)	0
Constipation	83 (24.9)	4 (1.2)	0	63 (19.1)	0	0
Headache	74 (22.2)	1 (0.3)	0	63 (19.1)	1 (0.3)	0
Hot flush	70 (21.0)	1 (0.3)	0	78 (23.6)	0	0
Back pain	66 (19.8)	7 (2.1)	0	58 (17.6)	1 (0.3)	0
Cough	65 (19.5)	0	NA	59 (17.9)	0	NA
Anemia§	62 (18.6)	3 (0.9)	1 (0.3)	15 (4.5)	4 (1.2)	0
Decreased appetite	62 (18.6)	5 (1.5)	0	50 (15.2)	1 (0.3)	0
Rash	57 (17.1)	2 (0.6)	0	26 (7.9)	0	0
Increased alanine aminotransferase	52 (15.6)	25 (7.5)	6 (1.8)	13 (3.9)	4 (1.2)	0
Increased aspartate aminotransferase	50 (15.0)	16 (4.8)	3 (0.9)	12 (3.6)	4 (1.2)	0

* Listed are events that were reported in at least 15% of the patients in any group. One event of interest (hypertension) fell below the reporting threshold listed here. NA denotes not applicable, since grade 4 cough and grade 3 and 4 alopecia are not included in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
† Four patients who were randomly assigned to the placebo group did not receive either placebo or letrozole.
‡ Neutropenia includes a decreased neutrophil count and granulocytopenia.
§ This category includes both anemia and a decreased hemoglobin level.

Table 5: Adverse Events (Hortobagyi et al. 2016)

2.3.3.7 Combination of Perjeta® (Pertuzumab) with Herceptin® (Trastuzumab) plus CDK4/6 inhibitor and endocrine therapy

In HER2-positive tumors, the dual antibody therapy plus an aromatase inhibitor led to a 21% rate of pCR in a neoadjuvant setting in ER+ cancers (Rimawi et al, J Clin Oncol 2013). In preclinical studies concomitant inhibition of CDK 4/6 and Trastuzumab led to synergistic antitumor activity (Goel S, et al. Cancer Cell 2016).The extent of early change and the persistence of Ki67 down-regulation are robust markers of the effects of endocrine treatments in hormonereceptors positive breast carcinomas in the setting of the neoadjuvant endocrine therapy (Sheri A, Dowsett M. Ann Oncol 2012).

Study NCT02530424 (NA-PHER 2) is an exploratory phase II study of trastuzumab and pertuzumab in combination with palbociclib (CDK 4/6i) and fulvestrant in the neo-adjuvant setting in patients with HER-positive and ER-positive breast cancer (BC). In this trial 23 women with invasive unilateral non metastatic ER-positive, HER2-positive BC and suitable for neoadjuvant therapy were treated with every 3 weeks Trastuzumab and Pertuzumab for 6 cycles combined with palbociclib 125 mg po q.d. x 21q4w and fulvestrant i.m. 500 mg, both given for 5 cycles.The primary endpoint of this study was characterization of Ki67 changes from baseline before therapy, at 2 weeks and at surgery.
It was shown that triple targeting of ER, HER2 and Rb in HER2+/ER+ BC treatment caused a significant and rapid decrease of Ki67 that was of larger magnitude after 2 weeks than at surgery irrespective of the recorded objective clinical response (Ki67 values from baseline after 2 weeks -24.5 ($P < 0.0001$) and -13.9 ($P=0.008$) from baseline to surgery). Treatment was well tolerated: no serious adverse events > grade 3 were reported. The most frequent G3 adverse events were neutropenia (26% of patients) and gastrointestinal disorders (17%) (Gianni L, et al. San Antonio Breast Cancer Symposium 2016).

2.3.4 Investigational Medicinal Product: Abraxane® (nab-Paclitaxel)

Nab-paclitaxel is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell.
Abraxane® is the first biologically interactive nanoparticle product leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic effects in normal tissue.
Preclinical studies comparing nab-paclitaxel to paclitaxel (paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with an MTD approximately 50% higher for nab-paclitaxel compared to paclitaxel. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, nab-paclitaxel was found to be markedly more efficacious than paclitaxel.

2.3.4.1 Clinical Experience

A phase III trial in patients with metastatic breast cancer compared nab-paclitaxel 260 mg/m2 to paclitaxel 175 mg/m2 given Q3W (Gradishar et al, 2005) i. Efficacy analyses were based on the ITT population. The ORR was significantly greater for nab-paclitaxel than for paclitaxel for all patients (33% v 19%, respectively; p = 0.001), patients who received second-line or greater therapy (27% v 13%, respectively; p = 0.006), and patients who had received prior anthracycline therapy in either the adjuvant/metastatic setting (34% v 18%, respectively; p = 0.002) or the metastatic setting, only (27% v 14%, respectively; p = 0.010). Tumor response rate was also significantly higher for nab-paclitaxel than for paclitaxel in patients with visceral metastases (34% v 19%, respectively; p = 0.002) and in patients aged younger than 65 years (34% v 19%, respectively; p < 0.001). ORR also was higher for nab-paclitaxel compared with standard paclitaxel in patients with non-visceral dominant lesions (34% v 19%, respectively) and in patients ≥ 65 years old (27% v 19%, respectively), but the results did not reach statistical significance because of the small number of patients in these subsets.
Median TTP was significantly longer with nab-paclitaxel than with paclitaxel for all patients (23.0 v 16.9 weeks, respectively; hazard ratio [HR] = 0.75; p = 0.006). There was a trend for greater median survival for all patients treated with nab-paclitaxel than with paclitaxel (65.0 v 55.7 weeks, respectively; p = 0.374). Although the difference was statistically significant in patients who received nab-paclitaxel, compared to paclitaxel, as second-line or greater therapy (56.4 v 46.7 weeks, respectively; HR = 0.73; p = .024).
The incidence of hypersensitivity reactions (any grade) was low for both arms (1% for nab-paclitaxel and 2% for paclitaxel). No severe (grade 3 or 4) treatment-related hypersensitivity reactions occurred in any of the patients in the nab-paclitaxel group despite the absence of premedication. Although the patients in the nab-paclitaxel group received an average paclitaxel dose-intensity 49% greater than that received by patients in the paclitaxel group, the incidence of treatment-related grade 4 neutropenia was significantly lower in the nab-paclitaxel group than in the paclitaxel group (9% v 22%, respectively; p < 0.001), with a higher mean neutrophil nadir (1.67 v 1.31x109/L, respectively; p = 0.046), suggesting that polyethylated castor oil may have contributed to this toxicity in patients who received standard (solventbased) paclitaxel. As expected with a higher dose of paclitaxel, treatment-related grade 3 sensory neuropathy occurred more frequently in the nab-paclitaxel arm than in the paclitaxel arm (10% v 2%, respectively; p < 0.001); however, these episodes improved with interruption of treatment to grade 2 or 1 in a median 22 days and were easily managed with treatment interruption and dose reduction. By day 28 after its first occurrence, the number of patients with persistent grade 3 sensory neuropathy was the same (n = 4) in both study arms. No episodes of motor neuropathy or grade 4 sensory neuropathy were reported in either group.

Nab-paclitaxel monotherapy is indicated for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard anthracycline containing therapy is not indicated.

Another randomized phase II trial compared nab-paclitaxel (300mg/m²) every 3 weeks with nab-paclitaxel 100mg/m² and 150mg/m² (3x weekly q4w) and docetaxel 100mg/m² three weekly. The 150 mg/m² nab-paclitaxel treated patients had a significant better overall response rate than the ones treated with docetaxel (74% vs 39%; p< 0.001). In addition, the both weekly regimen achieved a significant higher response rate than the three weekly regimen (63% vs 46%; p= 0.024; and 74% vs 46%; p=0.002). Similar results were obtained for the CBR (clinical benefit rate) for the investigator determined and the independent reviewer determined one. The progression free survival based on the independent review revealed a PFS for the three weekly nab-paclitaxel of 11 months compared to 12.8 months for 100mg/m² weekly and 12.9 months weekly for the 150mg/m² regimen and 7.5 months for docetaxel (overall p=0.048). Patients treated with nab-paclitaxel 150mg/m² in 3 of 4 weeks had a 50% lower risk of progression (HR 0.495; p=0.0065) compared to docetaxel. The neutropenia rate grade 3-4 was 44%; vs 25% vs 44% vs 95%. The rate of fatigue was highest with docetaxel 19% compared to 4% with nab-paclitaxel. The rate of sensory neutropathy was not different between the three treatment regimens.

2.3.4.2 Safety

So far, more than 2571 cancer patients have been enrolled in clinical studies with nab-paclitaxel. As described in the current IB, the most common adverse events (AEs) reported to date include myelosuppression, nausea and vomiting, diarrhea, mucositis, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, sensory neuropathy, bilirubin/liver enzyme elevations, allergic reactions, alopecia, asthenia, arthralgia, and myalgia. Treatment-related toxicities that resulted in dosing modifications typically involved neuropathia, myelosuppression or constitutional disorders such as fatigue or anorexia.

2.3.4.3 Summary

Solvent-based taxanes (paclitaxel, docetaxel) cause severe toxicities not only by the active agents itself but also by the solvents like cremophor. Nab-paclitaxel (Abraxane®) is a solvent-free formulation of paclitaxel encapsulated in albumin. It does not require premedication with corticosteroids or antihistamines to prevent the risk of solvent-mediated hypersensitivity reactions. This new formulation improves safety profile, allows higher dosing with shorter infusion duration, and produces higher tumor drug concentration. Nab-paclitaxel at a dose of 260 mg/m² was more effective than solvent-based paclitaxel at a dose of 175mg/m² (both given every 3 weeks) in patients with metastatic breast cancer and a phase II study suggested that weekly (3 weeks on, 1 week of) nab-paclitaxel at doses of 150 mg/m² was more effective in terms of response rate than 100mg/m² nab-paclitaxel or 3weekly docetaxel 100 mg/m² in a similar setting. Survival analysis revealed that 150mg/m² weekly nab-paclitaxel resulted in a significantly longer overall survival than 100 mg/m² weekly nab-paclitaxel and at trend towards a longer overall survival compared to 100mg/m² 3weekly docetaxel. Moreover, the onset of response was faster with 150mg/m² weekly nab-paclitaxel, showing best response already after 2.15 cycles. Tolerability of 150mg/m² weekly nab-paclitaxel appeared acceptable with 14% of patients revealing a sensory neuropathy of grade 3 and none of grade 4. Median time of onset of grade 3 sensory neuropathy was 23 weeks, which is at the end of the treatment duration planned in this protocol.

2.3.5 Investigational Medicinal Product: Halaven® (Eribulin)

Eribulin is a non-taxane microtubule dynamic inhibitor that was approved for the treatment of patients with ABC who have previously been treated with chemotherapies including both taxanes and anthracyclines. The EMBRACE study, a phase III, multicenter, international, open-label, randomized clinical trial of eribulin, provided evidence of clinically significant improvements in overall survival of patients treated with eribulin versus the treatment of physician's choice. Recent reports suggest that eribulin is a prime candidate for the treatment of HER2-positive ABC in patients who were previously treated with taxanes and anthracyclines.

A single-institute, single-arm, open-label, phase II trial involving patients with HER2-positive ABC who had previously received taxanes and trastuzumab in order to determine the efficacy and safety of eribulin mesylate in combination with Trastuzumab and pertuzumab. The study was carried out in the Cancer Institute Hospital of the Japanese Foundation for Cancer Research in Ariake, Japan.
A total of 30 patients (median age, 58 years; range, 31-76) were enrolled, with a median number of previous chemotherapy regimens of 3.5 (range: 1-9) in the metastatic setting. Pharmacokinetic parameters of eribulin in this combination were similar to previous reports of eribulin monotherapy.
Patients received 1.4 mg/m2 of eribulin mesylate (equivalent to 1.23 mg/m2 of eribulin as free base) administered intravenouslyover 5 min on days 1 and 8 of each 21-day cycle. Dose reductions for eribulin, but not for pertuzumab and trastuzumab, were permitted. Two-step dose reductions to 1.1 mg/m2 and 0.7 mg/m2 were allowed before consideration of study treatment discontinuation. Dose interruptions were allowed for eribulin treatment, but not for trastuzumab or pertuzumab. Patients receiving pertuzumab and trastuzumab were given a fixed loading dose of 840 mg Pertuzumab followed by 420 mg every 3 weeks, and a loading dose of 8 mg/kg trastuzumab followed by a maintenance dose of 6 mg/kg every 3 weeks. This regimen was continued until the occurrence of progressive disease (PD), as assessed by the investigator on the basis of radiographic, cytologic, or photographic evidence, or until development of toxic effects that could not be effectively managed. All drugs were administered intravenously. In case of discontinuation of eribulin due to toxic effects, pertuzumab and trastuzumab were continued until PD, development of unacceptable toxic effects, or withdrawal of consent. Eribulin could be continued as monotherapyif pertuzumab and trastuzumab were discontinued, and vice versa.
The primary endpoint was anti-tumor activity of eribulin in combination with pertuzumab and trastuzumab, as assessed by investigators for objective response rate (ORR) using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Secondary endpoints included PFS, safety, and PK of eribulin.
Results: ORR was 34.8% (95% CI: 16.4-57.3, n = 23), and median progression-free survival was 42.6 weeks (95% CI: 20.3-51.9, n = 30). Clinical benefit rate was 60.9% (95% CI: 16.4-57.3). The most common grade 3/4 adverse event was neutropenia in 20 patients (66.7%). A dose reduction of eribulin was required in 27 patients due to adverse events, particularly grade 3 neutropenia.
Eribulin in combination with pertuzumab and trastuzumab was well tolerated in heavily pretreated patients. Eribulin may be a viable treatment option when used in combination with Pertuzumab and trastuzumab for HER2-positive ABC patients

2.4 Study Rationale

Especially for diseases that are not curable such as metastatic breast cancer, the maintenance of quality of life is one of the main aims of treatments. Adverse events are well-known side effects of any cytostatic treatment and particularly adverse events of grade 3 or higher seriously impact the patients' quality of life. Therefore, new treatment options are developed that should stop or at least slow down metastatic spread of cancer without causing negative side effects in terms of high-grade adverse events.
In breast cancer patients with HER2-positve disease a HER2-targeted therapy is recommended. Trastuzumab as anti-HER2 humanized monoclonal antibody in addition to chemotherapy improves progression-free and overall survival, and the efficacy and tolerability of the combination of trastuzumab with different chemotherapy regimens has been evaluated in several clinical trials.
The randomized, double-blind, placebo-controlled, phase III CLEOPATRA trial demonstrated superior efficacy of a dual HER2 targeted therapy as first-line treatment for HER2 positive metastatic breast cancer. The combination of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel significantly prolonged both progression-free survival (Baselga et al. 2012) and overall survival (Swain et al. 2013a), with no increase in cardiac toxic effects (Swain et al. 2013b).
For patients with hormone-receptor positive and HER2 positive MBC the combination of HER2-targeted therapy with endocrine therapy has already been proven to be an effective and in many cases valuable alternative to the combination of HER2-targeted therapy with chemotherapy. The high relevance of HER2-neu-targeted/endocrine treatment combinations derives from the fact that potential chemotherapy-related toxicity can be avoided, which in turn positively affects quality of life.
In the eLEcTRA trial the combination of trastuzumab and letrozole was shown to be a safe and effective treatment option for these patients (Huober et al. 2012). Similar results were obtained for the combination of trastuzumab plus anastrozole in the TAnDEM trial (Kaufman et al. 2009).
The NA-PHER2 trial of trastuzumab and pertuzumab plus CDK 4/6inhibitor palbociclib and fulvestrant in the neoadjuvant setting showed promising clinical responses and good tolerability without new safety issues of the triple combination (Gianni et al., SABCS 2016). We assume that the CDK4/6 inhibitor ribociclib will modulate the endocrine resistance and potentiate the benefits of dual HER2-targeted therapy in HER2+/ER+ MBC.
The combination of dual HER2-targeted therapy with trastuzumab and pertuzumab plus standard endocrine therapy (plus ribociclib after the amendment comes into effect) might offer an even better and effective treatment option in patients with HER2 positive and hormone-receptor positive MBC. However, this combination has not been evaluated in the metastatic setting and compared to the combination of dual HER2-targeted therapy plus chemotherapy in a prospective randomized phase III clinical trial.
Therefore in this clinical trial patients with MBC will be randomized to receive either trastuzumab and pertuzumab with chemotherapy or with endocrine-based therapy (see 3.1 and Figure 4). Thus, direct comparison of the two treatment options is possible.

The primary objective of this study (defined before the amendment coming into effect) is to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus standard endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy followed by maintenance treatment with dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus standard endocrine therapy in patients with HER2-positive, hormone-receptor positive metastatic breast cancer. Tolerability will be assessed by the proportion of patients experiencing any adverse event (as defined by the modified adverse event score) during the treatment period. As the primary objective of this trial is to evaluate the occurrence of adverse events that have a high impact on the patients' quality of life, we developed a modified adverse event score that includes all adverse events grade 3 or higher with the exception of neutropenia, which is only included if rated grade 4, and

alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher. In our opinion, an analysis of the occurrence of adverse events as defined by this modified adverse event score better reflects the clinical, physiological and psychological impact of adverse events on the patients' quality of life than using an overall cut-off of grade 3 or higher for all adverse events irrespective of the type.

With the amendment coming into effect, the CDK4/6 inhibitor Kisquali® (ribociclib) will be added to both therapy arms. Thus, the new primary objective of this study is to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisquali® (ribociclib) and standard endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy (followed by endocrine therapy plus Kisquali® (ribociclib) in combination with trastuzumab and pertuzumab as maintenance therapy during follow-up periode) in patients with HER2-positive, hormone-receptor positive metastatic breast cancer. Tolerability will be assessed by the proportion of patients experiencing any adverse event (as defined by the modified adverse event score) during the treatment period.

The key secondary objective of this study is to compare quality-adjusted survival (QAS) between the two treatment arms (dual HER2-targeted plus chemotherapy vs. dual HER2-targeted plus endocrine-based therapy). Single efficacy endpoints such as progression-free survival measure the length of time between clinical events but do not consider the value of that time to the patient. However, the value of time as perceived by the patients themselves is particularly relevant in diseases that have relatively short expected survival and the intent of treatment is palliative rather than curative such as advanced or metastatic cancer. QAS as measured using the Q-TWiST method provides a single metric value that is a composite measure of quantity of survival time and quality of survival as assessed by the patients themselves. Q-TWiST analyses account for possible trade-offs between quantity and quality of life (e.g. prolonged time to progression at the cost of higher toxicity, which adversely affects quality of life), and provide an excellent tool to evaluate whether two treatment options differ with regard to the overall perceived value to the patients (Goldhirsch et al. 1989; Glasziou et al. 1990; Gelber et al. 1993). Thus, Q-TWiST provides a measure of overall benefit not necessarily apparent from separate assessments of efficacy and/or safety.

2.5 Analysis of Circulating Tumor Cells

Circulating tumor cells (CTCs) are present in about 65-85% of patients with metastatic breast cancer (Fehm et al. 2010, Botteri et al. 2010, Pierga et al. 2012). The results of several studies imply that presence of CTCs before therapy start and change in CTC counts during therapy might be good indicators of survival time and therapy success (Cristofanilli et al. 2004; Hayes et al. 2006; Liu et al. 2009; Bidard et al. 2010; Giuliano et al. 2011; Pierga et al. 2012). As part of the translational research program, prevalence and number of CTCs will be determined before and at different time points after initiation of palliative treatment including the time of progression using the FDA-approved CellSearch® System (Janssen Diagnostics). The value of CTC prevalence, number and dynamic in assessing therapy efficacy in patients with HER2-positive, hormone-receptor positive metastatic breast cancer will be evaluated.

In addition to the quantitative assessment of CTCs, the expression of the markers estrogen receptor and HER2, on isolated CTCs will be determined using the CellSearch® system (as described by Paoletti et al. 2011). Based on the level of expression for these markers and the proportion of CTCs showing such marker expression, an endocrine responsiveness score (ERS) will be calculated and its predictive value for assessing therapy efficacy will be determined.

2.6 Risk/Benefit Assessment

Risks patients may be exposed to due to study participation
If a patient is treated with dual HER2-targeted therapy with trastuzumab and pertuzumab, the side effects may cause risks according to the well-known spectrum of adverse effects of this dual HER2-targeted therapy. The frequency of adverse effects is well published, and there is a very small risk of life threatening side effects (see Roche Investigator's Brochure Perjeta®, 13th Version, February 2014).
Except for blood sampling for CTC assessments and quality of life evaluations there are no additional impairments due to study participation.

Benefits accruing to patients by study participation
If patients are treated with dual HER2-targeted therapy with Herceptin® and pertuzumab in combination with either chemotherapy or endocrine-based therapy, there is a considerable chance that they are treated more effectively and profit from prolonged progression free and/or overall survival compared to treatment combining single HER2-targeted therapy using Herceptin® alone with either chemotherapy or endocrine-based therapy.

Scientific benefit
If the combination of dual HER2-targeted therapy using trastuzumab and pertuzumab with either chemotherapy or endocrine-based therapy is shown to be efficacious, this study will lead to improved treatment of HER2 positive and hormone-receptor positive metastatic breast cancer. Furthermore, if adverse events as defined by the modified adverse event score occur significantly less frequently in patients treated with dual HER2-targeted plus ribociclib and standard endocrine therapy as compared to patients treated with dual HER2-targeted plus chemotherapy followed by maintenance therapy with endocrine therapy in combination with dual blockade and ribociclib, the study will provide clinicians and patients with a suitable treatment option for patients with HER2 positive and hormone-receptor positive metastatic breast cancer, that focuses on the enhancement of quality of life in this palliative setting of the disease. The analysis of quality-adjusted survival using the Q-TWiST method will provide further important information regarding the value and benefit of different treatment options with regard to the quality of life as perceived by the patients themselves.
The data gained in the translational part of the study will increase the knowledge of the role of CTC dynamics and the endocrine responsiveness score of CTCs as assessed at different time points for prognosis and evaluation of therapy efficacy in metastasizing breast cancer.

Risk/benefit assessment
Anticancer therapy generally is associated with considerable side effects. The potential benefit of increased efficacy and/or enhanced quality of life as result of a treatment with dual HER2-targeted therapy using Herceptin® and pertuzumab combined with either chemotherapy or endocrine therapy would be of high relevance given the unfavorable prognosis and palliative nature of MBC. Taking into account the possible benefits resulting from the study, the risks of the study appear acceptable.

2.7 Quality of Life

Quality of life (QoL) is of high relevance to metastatic cancer patients. From the patient's perspective it measures possible drawbacks and – beyond prolongation of survival – possible benefits from an intervention. It provides important additional information compared to measuring adverse events alone (Huschka et al. 2007).
In addition to the analysis of quality-adjusted survival based on the Q-TWiST method (see 2.4), quality of life will be analysed in more detail using the EORTC QLQ-C30 core questionnaire and the supplementary breast cancer module QLQ-BR23 as measuring tool. These questionnaires are designed to capture the multidimensionality of QoL in metastatic breast cancer. The EORTC QLQ-C30 and QLQ-BR23 are widely used, cancer specific health-related

QoL questionnaires which are well accepted by patients (Aaronson et al. 1993, Conroy et al. 2004). The EORTC QLQ-C30 core questionnaire comprises 30 questions assessing five functional subscales (physical, role, cognitive, emotional, social), three multi-item symptom subscales (fatigue, nausea and vomiting, and pain), six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial impact) and a global health measure (physical condition and global QoL). The QLQ-BR23 breast-cancer module comprises 23 questions and incorporates five multi-item scales (systemic therapy side effects, arm symptoms, breast symptoms, body image, sexual functioning) and three single-item questions (sexual enjoyment, hair loss, future perspective). The questionnaires use 4 and 7-point scales. For evaluation each scale is linearly transformed into a scale ranging from 0 to 100. Convergence and criterion validity has been demonstrated for this questionnaire in metastatic breast cancer (Bottomlay et al. 2004, McLachlan et al. 1998) and reliability is adequate (Aaronson et al. 1993, Hjermstad et al. 1995). The EORTC QLQ-C30 + BR23 has been shown to be responsive to change associated with chemotherapy and with disease progression (Osoba et al. 1998, Lemieux et al. 2007). The questionnaire is available in German (see APPENDIX – Quality of life assessments)

3 Investigational Plan

3.1 Overall Study Design and Plan

This is a prospective, open, multicentre, randomized phase IIIa clinical trial.

3.1.1 Study Design and Plan Protocol Version 1.1 03.06.2015

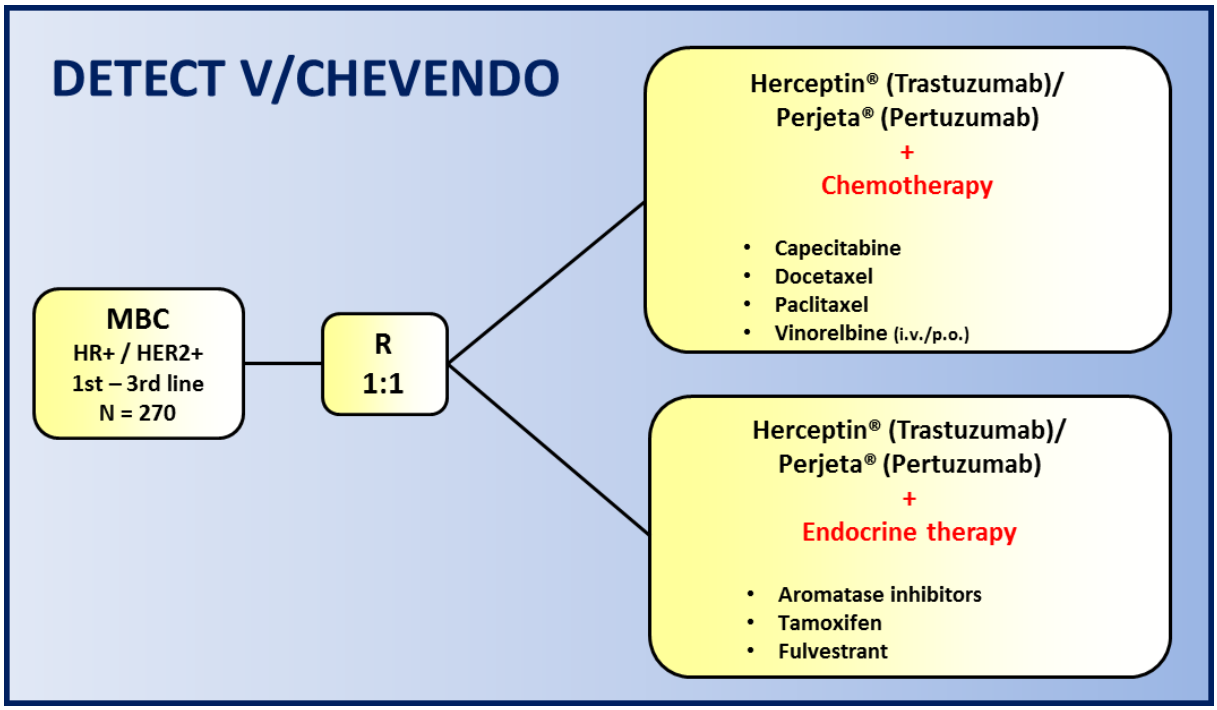


Figure 3: Clinical trial design

After randomization in the chemotherapy or endocrine therapy arm, it is on the discretion oft he investigator to decide about the drug, which has to be given in combination with Herceptin®/ Perjeta®. A switch between the two randomization arms is not allowed.

A change between drugs within one randomization arm due to drug related toxicities is also not allowed.

Randomization

Patients with HER2-positive, hormone-receptor positive MBC, who fulfill all inclusion criteria and exclusion criteria will be randomized 1:1 into the following treatment arms:

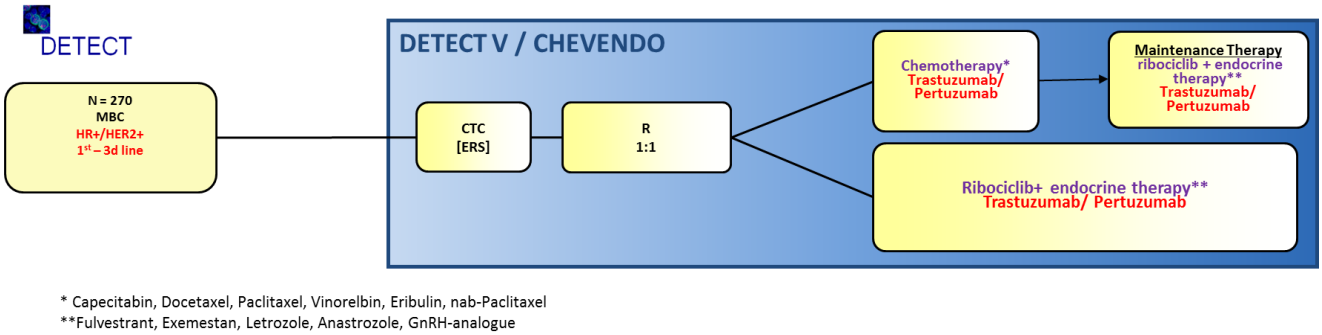
- Herceptin® + Perjeta® combined with mono-chemotherapy
- Herceptin® + Perjeta® combined with endocrine therapy

Before randomization, the cohort will be stratified using the following factors

- Line of chemotherapy treatment (first line versus higher) In case that the percentage of patients with no previous treatment for advanced
- Line of chemotherapy treatment (first line versus higher) In case that the percentage of patients with no previous treatment for advanced disease (first line patients) will be more than 40%, recruitment into the study will be adjusted and limited to further line patients
- Presence of visceral (pulmonary and hepatic) metastases (yes versus no).
- Previous therapy with trastuzumab (yes versus no)

- Previous therapy with pertuzumab (yes or no)
- Stratified randomization will be carried-out using permuted blocks within stratum.

3.1.2 Study Design and Plan With Addition of Kisqali® (ribocilib) to both treatment Arms



* Capecitabin, Docetaxel, Paclitaxel, Vinorelbin, Eribulin, nab-Paclitaxel
**Fulvestrant, Exemestan, Letrozole, Anastrozole, GnRH-analogue

Figure 4: Clinical trial design

After randomization in the chemotherapy or endocrine-based therapy arm, it is on the discretion of the investigator to decide about the drug, which has to be given in combination with Herceptin®/Perjeta® and Kisqali® (ribociclib). A switch between the two randomization arms is not allowed. A change between drugs within one randomization arm due to drug related toxicities is also not allowed.

Randomization

Patients with HER2-positive, hormone-receptor positive MBC, who fulfill all inclusion criteria and exclusion criteria will be randomized 1:1 into the following treatment arms:

- Arm A: Herceptin® + Perjeta® combined with mono-chemotherapy, followed by maintenance therapy with Herceptin® and Perjeta® plus Kisqali® and endocrine therapy
- Arm B: Herceptin® + Perjeta® combined with endocrine therapy plus Kisqali®

Before randomization, the cohort will be stratified using the following factors:

- Line of chemotherapy treatment (first line versus higher) In case that the percentage of patients with no previous treatment for advanced disease (first line patients) will be more than 60%, recruitment into the study will be adjusted and limited to further line patients.
- Presence of pulmonary and/or hepatic metastases (yes versus no).
- Previous therapy with trastuzumab (yes versus no)
- Previos therapy with pertuzumab (yes versus no)

Stratified randomization will be carried-out using permuted blocks within stratum.

Randomization is performed online via an electronic case report form (eCRF) and is possible 24 hours a day.

3.1.3. Number of Patients

270 women suffering from HER2-positive, hormone-receptor positive MBC will be included.

3.1.4. Planned Study Timelines

Enrolment start date (FPI):	Q3 / 2015
Enrolment finish date (LPI):	Q2 / 2020
Treatment period end date (LP off treatment):	Q2 / 2021
Follow-up-period:	24 months
End of follow-up:	Q2 / 2023

3.2 Study Objectives

3.2.1 Primary Objective

Primary objective (before the amendment coming into effect):
The primary objective of this study is to assess tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy in patients with HER2-positive, hormone-receptor positive metastatic breast cancer. Tolerability will be assessed by the proportion of patients experiencing any adverse event (as defined by the modified adverse event score) during the treatment period.
The modified adverse event score includes all adverse events grade 3 or higher with the exception of neutropenia, which is only included if rated grade 4, and alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher.

New primary objective:
With the amendment coming into effect, the CDK4/6 inhibitor Kisquali® (ribociclib) is added to both therapy arms. Thus, the new primary objective of this study is to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisquali® (ribociclib) and standard endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy (followed by endocrine therapy plus ribociclib in combination with trastuzumab and pertuzumab as maintenance therapy) in patients with HER2-positive, hormone-receptor positive metastatic breast cancer. Tolerability will be assessed by the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period.
The modified adverse event score includes all adverse events grade 3 or higher with the exception of neutropenia, which is only included if rated grade 4, and alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher.

3.2.2 Secondary Objectives

Main secondary objectives:
The main secondary objectives of this study are

- to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy for patients that were randomized before the amendment (i.e. the addition of ribociclib to both treatment arms) coming into effect. Tolerability will be assessed by the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period.
- to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy for all patients that were randomized (irrespectively of whether they

were randomized before or after the amendment – the addition of ribociclib to both treatment arms - coming into effect). Tolerability will be assessed by the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period.

Additional secondary objectives:

- to account for the addition of Kisquali® (ribociclib), the primary analysis will be repeated (as secondary explorative analysis) using a specific modified adverse event score for the ribociclib cohort that includes nausea, vomiting, diarrhea and stomatitis grade 2 (in addition to the adverse events included in the modified adverse event score as used for the primary analysis)
- to assess quality-adjusted survival (as assessed by the Q-TWiST method) and to compare it between the two treatment arms
- to compare efficacy between the two treatment arms as assessed by overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) based on local assessment according to RECIST v1.1 in each cohort
- to assess the incidence of CNS metastases, evaluated by contrast-enhanced computer tomography (CT) or, preferably, magnetic resonance imaging (MRI) according to RECIST v1.1 based on local assessment
- to assess additional aspects of quality of life based on the evaluation of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires
- to determine presence and number of CTCs in the peripheral blood at baseline and at different time points after the start of palliative treatment including the time of progression, and to assess the value of CTCs as indicator for therapy success
- to determine the endocrine responsiveness score (ERS) of CTCs at baseline and at different time points after the start of palliative treatment including the time of progression, and to assess the value of the ERS as indicator for therapy success
- to evaluate and compare toxicity of both treatment arms
- to evaluate the safety and tolerability of the study treatments (all grades, all events)

3.2.3 Primary Endpoint

The primary endpoint is defined as the proportion of patients that experience any adverse events (as defined by the modified adverse event score and assessed based on NCI CTCAE Version 4.03) during the treatment period.

The modified adverse event score includes all adverse events grade 3 or higher with the exception of neutropenia, which is only included if rated grade 4, and alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher.

3.2.4 Secondary Endpoints

Secondary endpoints are

1. Specific modified adverse event score including nausea, vomiting, diarrhea and stomatitis grade 2 (in addition to the adverse events included in the modified adverse event score as used for the primary analysis)
2. Quality-adjusted survival (as assessed by the Q-TWiST method), with the utility scores for the different health states being prospectively determined in the clinical trial subjects based on the EORTC QOL C30 questionnaire
3. Progression free survival (PFS): Time interval from randomization until progressive disease (PD) or death from any cause, whichever comes first (to be assessed by investigator)

4. Overall response rate (ORR): Rate of complete (CR) and partial responses (PR) in patients with whom target lesions were defined
5. Clinical benefit rate: Rate of patients who were assessed PR or CR or who had stable disease (SD) for at least 6 months
6. Overall survival (OS): Time from randomization until death of any cause
7. Quality of life (QoL): As assessed by evaluation of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires
8. Prevalence of CTCs at baseline and at different time points after the start of palliative treatment including the time of progression (as assessed using the CellSearch® System)
9. Endocrine responsiveness score (ERS) of CTCs at baseline and at different time points after the start of palliative treatment including the time of progression

(CR, PR, SD, and PD are defined according to the RECIST Version 1.1 criteria)

3.3 Study Population and Justification of Choice of Gender

The selection of patients occurs through the investigator according to the inclusion and exclusion criteria after informing the patient written and orally about the study and after the patient has signed the informed consent. Since breast cancer is primarily a disease of women, only women will be enrolled within this clinical trial. However, pregnant or breast-feeding women are excluded from participation.

3.3.1 Inclusion Criteria

Patients will be **included** in the study only if they meet **all** the following criteria:

- Signed, written informed consent in study participation
- The primary tumor and/or biopsies from metastatic sites or locoregional recurrences have been confirmed as HER2-positive (FISH-positive or IHC 3+) and hormone receptor positive breast cancer by histopathology according to local testing
- Metastatic breast cancer or locally advanced BC, which cannot be treated by surgery or radiotherapy only
- Pre- and postmenopausal women are allowed
- No more than two prior chemotherapies for metastatic disease
- No more than two prior anti-HER2 therapies for metastatic disease
- Pertuzumab retreatment is allowed if prior adjuvant /neoadjuvant pertuzumab treatment was finished 12 months before
- At least one measurable lesion assessable using standard techniques by Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v1.1)
- Tumor evaluation according to RECIST version 1.1 has been performed within 4 weeks before randomization based on local assessment
- Age ≥ 18 years
- Standard 12-lead ECG values assessed by the local laboratory:
  - QTcF interval at screening < 450 msec (using Fridericia's correction)
  - Resting heart rate 50-90 bpm
- Left ventricular cardiac ejection fraction (LVEF) ≥ 50% at baseline (as measured by echocardiogram)
- ECOG Score ≤ 2

- Adequate organ function within 14 days before randomization, evidenced by the following laboratory results below:

absolute neutrophil count	≥ 1500 cells/µL,
platelet count	≥ 100000 cells/µL,
hemoglobin	≥ 9 g/dL,
ALT (SGPT)	≤ 2.0 × ULN (≤ 3.0 × ULN in case of liver metastases)
AST (SGOT)	≤ 2.0 × ULN (≤ 3.0 × ULN in case of liver metastases)
bilirubin	≤ 1.5 × ULN (with the exception of Gilbert's syndrome)
creatinine	≤ 2.0 mg/dl or 177µmol/L
INR	≤ 1,5

- Patients must have the following laboratory values within normal limits or corrected to within normal limits with supplemets before the first dose of study medication:
  -Sodium
  -Potassium
  -Total calcium
- In case of patients of child bearing potential:

  Negative serum pregnancy test at baseline (within 7 days prior to randomization) and agreement to remain abstinent (if it is in line with the preferred and usual lifestyle) or use single or combined non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of study treatment.

3.3.2 Exclusion Criteria

Patients will be **excluded** from the study for **any** of the following reasons:

- History of hypersensitivity reactions attributed to trastuzumab or pertuzumab, ribociclib or to other components of drug formulation
- Mandatory need for cytostatic treatment at time of study entry based on clinical judgment and relevant guidelines
- Known CNS metastases
- Any concurrent severe, uncontrolled systemic disease, social or psychiatric condition that might interfere with the planned treatment and with the patient's adherence to the protocol
- Progression on prior Pertuzumab therapy
- Treatment with Pertuzumab within the last 12 months
- Prior treatment with any mTOR- or CDK4/6-inhibitor
- Treatment with any other investigational agents during trial
- Hypersensitivity to lecithin (soya) or peanuts
- Life expectancy < 6 months
- Patients with pre-existing grade ≥2 peripheral neuropathy are excluded from taxane-based chemotherapy
- History of serious cardiac disease, including but not confined to:

  - history of documented heart failure or systolic dysfunction (LVEF < 50%)

  - high-risk uncontrolled arrhythmias i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block)

  - angina pectoris requiring anti-anginal medication

  - clinically significant valvular heart disease

- evidence of transmural infarction on ECG
- poorly controlled hypertension (e.g., systolic >180 mm Hg or diastolic >100 mm Hg)
- any other cardiac condition, which in the opinion of the treating physician would make this protocol unreasonably hazardous for the patient

- Dyspnea at rest or other diseases that require continuous oxygen therapy
- Patients with poorly controlled diabetes or with evidence of clinically significant diabetic vascular complications
- Patients with known infection with HIV, hepatitis B virus, or hepatitis C virus
- Male patients
- Pregnant, lactating or women of childbearing potential without a negative pregnancy test (serum) within 7 days prior to randomization, irrespective of the method of contraception used
- Medical or psychological conditions that would not permit the subject to complete the study or sign informed consent
- Participation in another clinical study within the 30 days before registration
- Legal incapacity or limited legal capacity

3.3.3 Enrolment of Patients

Patients are screened to ensure that they meet the inclusion and exclusion criteria and are enrolled by online registration.
Online randomization is possible 24 hours a day. After the registration form 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.
After randomization treatment can be instituted within a maximum interval of 14 days.

4 Study Medication

4.1 Investigational Medicinal Product Perjeta® (Pertuzumab)

4.1.1 Pharmaceutical Information

Pharmaceutical form:
Perjeta® (pertuzumab) is a recombinant, humanized monoclonal antibody based on the human IgG1 (κ) framework sequences and consists of two heavy chains (449 residues) and two light chains (214 residues).
Perjeta® is produced in Chinese hamster ovary (CHO) cell cultures.

Perjeta® drug product is provided as a single use formulation containing 30 mg/mL pertuzumab in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20. Each 20 mL vial contains 420 mg of pertuzumab (14.0 mL/vial).

Mechanism of action:
Like trastuzumab, pertuzumab is directed against the extracellular domain of HER2. However, it differs from trastuzumab in the epitope-binding regions of the light chain (12 amino acid differences) and heavy chain (29 amino acid differences). As a result, pertuzumab binds to an epitope within subdomain 2 of HER2 while the epitope for trastuzumab is localized to subdomain 4.

Storage and stability:
Upon receipt, Perjeta® vials are to be refrigerated at 2°C–8°C (36°F–46°F) until use.
Perjeta® vials should not be used beyond the expiration date provided by the manufacturer. Because the formulation does not contain a preservative, the vial seal may only be punctured once. Any remaining solution should be discarded. Vial contents should be protected from light, and should not be frozen.

The solution of Perjeta® for infusion, diluted in PVC or non-PVC polyolefin bags containing 0.9% sodium chloride Injection may be stored for up to 24 hours prior to use. Diluted Perjeta® has been shown to be stable for up to 24 hours at a temperature range of 2°C–25°C. However, since diluted Perjeta® contains no preservative, the diluted solution should be stored refrigerated (2°C–8°C).

Route of administration:
intravenous infusion

Suspension preparation:
14 ml concentrated solution containing 420 mg pertuzumab should be diluted with 250 ml 0.9% sodium chloride.
Diluted Perjeta® is administered as intravenous infusion on d1 of each treatment cycle. One treatment cycle lasts 21 days.

Manufacturer:
Roche Pharma AG

4.1.2 Licensed Indication

Perjeta® (pertuzumab) is approved in combination with Herceptin® (trastuzumab) and docetaxel for the therapy of patients with HER2-positive MBC who have no prior anti-Her2 therapy or no chemotherapy treatment for the advanced disease.

4.1.3 Contraindications

Hypersensitivity against pertuzumab or one of the other components of the concentrated solution.

4.1.4 Safety

For safety reasons, intravenous administration of Perjeta® should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. Patients should be monitored during and following completion of each Perjeta® infusion for any adverse effects. Since there is the potential for delayed onset infusion-associated reactions, patients should be warned of this possibility and instructed to contact the treating physician with any concerns.
Unless otherwise specified in the protocol, the initial Perjeta® dose should be administered over 60 minutes (± 10 minutes). If prior infusions were well tolerated, subsequent doses may be administered over 30 minutes (± 10 minutes). Patients should be observed for fever, chills, and other infusion-associated symptoms for at least 60 minutes after the first infusion and for 30 minutes after subsequent infusions If symptoms occur, the infusion should be slowed, interrupted, or discontinued. When the patient's symptoms have completely resolved, the infusion may be continued at 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full dose during the next cycle. Patients who experience Perjeta® infusion-associated symptoms may be premedicated for subsequent infusions.
Adverse reactions observed with administration of Perjeta® in combination with Herceptin® and docetaxel are given in the following Table 4.
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 study participants.

System organ class	Very frequently occurring adverse reactions (≥1/10)	Frequently occurring adverse reactions (≥ 1/100, < 1/10)	Occasionally occurring adverse reactions (≥1/1.000 bis <1/100
Infections and infestations	Upper respiratory tract infection, Nasopharyngitis	Paronychia	
Blood and lymphatic system disorders	Febrile neutropenia, Neutropenia, Anaemia, Leukopenia		
Immune System Disorders	Hypersensitivity/ Drug hypersensititvity, Infusion-related reactions(Cytokine release syndrome)		
Metabolism and nutrition disorders	Decreased appetite		
Psychiatric disorders	Insomnia		
Nervous system disorders	Neuropathy peripheral, Headache, Dysgeusia	Peripheral sensory neuropathy, Dizziness	
Eye disorders		Lacrimation increased	

System organ class	Very frequently occurring adverse reactions (≥1/10)	Frequently occurring adverse reactions (≥ 1/100, < 1/10)	Occasionally occurring adverse reactions (≥1/1.000 bis <1/100
Cardiac Disorders		Left ventricular dysfunction, Symptomatic left ventricular dysfunction	
Respiratory, thoracic and mediastinal disorders	Cough	Pleural effusion, Dyspnoea	Interstitial lung disease
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Constipation, Stomatitis, Dyspepsia		
Skin and subcutaneous tissue	Alopecia, Rash, Nail disorder,	Pruritus, Dry skin	
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia		
General disorders and administration site conditions	Fatigue, Asthenia, Oedema peripheral, Mucositis/Mucosal inflammation, Pain, Pyrexia	Chills	

Table 6: Known reactions observed with Perjeta® (pertuzumab)

Please also refer to the most current version of Summary of medicinal Product Characteristics (SmPC) and Investigator's Brochure (IB).

4.1.5 Supply

Perjeta® is provided free of charge by Roche if used outside the official EMA label. The provided study medication will be labelled study-specific and not patient-specific.
Investigator's request of Perjeta® will be done through the eCRF (initial order automatically with randomization, follow up orders as required). Manufacturer is Roche Pharma AG, Emil-Barell-Str.1, 79639 Grenzach Wyhlen.

Perjeta® will be prescribed in the licensed combination (first line-treatment with Perjeta® + Herceptin® + docetaxel).

4.1.6 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 used by each subject. At the end of the trial, all unused trial medication and all medication containers will be completely returned to Roche. Also expired or for other reasons unused study medication during the trial will be returned to Roche (IMP Return Form (PD 101)). Not fully expended vials can be 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:
On receipt of study medication: Confirmation of receipt including date, amount, batch number, information on potential damage and signature of the responsible person. With every shipment Roche will provide an appropriate form, which must be filled out, faxed back to Roche (FAX.-Nr.: 07624-14-3846 and filed at site) and filed in the ISF.
On dispensing study medication to the patient: patient identification number, date, batch number, number of vials used, signature of the responsible staff member.
(Abholfax und PD 101 Formular von Roche an Apotheken)
Drug accountability is documented in the eCRF.

4.2 Combination Drug Herceptin® (Trastuzumab)

4.2.1 Pharmaceutical Information

Pharmaceutical form:
Herceptin® (trastuzumab) is a recombinant humanized anti-p185^{HER2}monoclonal antibody which is produced in Chinese hamster ovary (CHO) cell cultures.
Herceptin® is provided as powder for concentrate for solution for injection (intravenous [iv] administration) and as solution for injection (for subcutaneous [sc] administration):

- Herceptin® powder for concentrate for solution for injection (iv administration) is supplied commercially as a lyophilized formulation in single dose (150 mg) vials. It is formulated in histidine/histidine-HCl, α,α-trehalose dihydrate, and polysorbate 20.
- Herceptin® solution for injection (sc administration) is supplied as a ready-to-use liquid formulation with a nominal content of 600 mg/5 ml trastuzumab, rHuPH20 (human recombinant hyaluronidase manufactured in a CHO cell line), a permeation enhancer to allow SC administration of higher volumes, histidine/histidine-HCl (buffer), α,α-trehalose dihydrate (bulking agent), methionine (stabilizer), and polysorbate 20 (stabilizer/emulsifier) in water for injection at a pH of 5.5 ± 0.6.

Mechanism of action:
Trastuzumab binds specifically and with high affinity to the extracellular domain of HER2. Binding inhibits ligand-independent HER2-signaling and also prevents proteolytic cleavage of the extracellular domain, thus prohibiting activation HER2. As a result proliferation of human tumor cells overexpressing HER2 is inhibited. Furthermore by attaching to HER2, trastuzumab activates cells of the immune system, which then kill the tumor cells.

Storage and stability:
The recommended storage conditions of Herceptin® powder and solution are 2-8°C, and protected from light.
Herceptin® 150 mg powder:
The reconstituted solution is stable for 48 hours at 2-8°C. Freezing is not allowed.

Before application, the product should be allowed to equilibrate to ambient temperature, at least one hour and not more than 6 hours at ambient temperature (ambient temperature should not exceed 30°C).

Route of administration:
iv. infusion

Suspension preparation:
Herceptin® iv administration:
Reconstitution in 7.2 ml sterile water yields 7.4-ml solution for single-dose use, containing ~21 mg/mL trastuzumab at a pH of ~6.0.

A volume overfill of 4% ensures that the labeled dose of 150 mg can be withdrawn from each vial. Reconstituted trastuzumab should be added to 250 mL of 0.9% sodium chloride for injection. This formulation must be infused immediately after reconstitution.

Determination of necessary volume:

Volume (ml) = body weight (kg) × Dose (initial 8 mg/kg or 6 mg/kg for further infusions)Trastuzumab is

Dose = initial 8 mg/kg or 6 mg/kg for further infusions / 21 mg/ml (concentration of reconstituted solution)

Manufacturer:
Roche Pharma AG

4.2.2 Licensed Indication

Herceptin® is indicated for patients with MBC whose tumors overexpress the HER2 protein

- as monotherapy for the treatment of patients who have received at least two chemotherapy regimens for their metastatic disease.
  Prior chemotherapy regimens have to include an anthracycline and a taxan, unless these drugs are not suitable for the patient.
  Patients with ER-/PR-positive cancer must have received a previous treatment with hormones, unless this treatment is unsuitable for the patients.
- in combination with an aromatase inhibitor for the treatment of patients with hormone-receptor positive metastatic breast cancer, and
- in combination with paclitaxel or docetaxel for the treatment of patients who have not received chemotherapy for their metastatic disease
- in combination with Perjeta® (pertuzumab) and docetaxel for the therapy of patients with HER2-positive MBC who have no prior anti-Her2 therapy or no chemotherapy treatment for the advanced disease.
- in combination with lapatinib for the treatment of patients with hormone-receptor negative (HR-) metastatic disease that have progressed on prior trastuzumab therapy(ies) in combination with chemotherapy

4.2.3 Contraindications

- Known hypersensitivity to trastuzumab or to any other component of the product or to mouse proteins
- Severe dyspnea at rest caused by complications of the advanced cancer disease or which needs supporting oxygen therapy

4.2.4 Safety

The most common or serious side effects with Herceptin® are heart problems, infections, lung and blood problems, and administration-related reactions. Please refer also to the most current version of SmPC and IB.

4.3 Investigational Medicinal Product Kisqali® (Ribociclib)

4.3.1 Pharmaceutical Information

Pharmaceutical form:
Ribociclib is formulated as film-coated tablets of 200 mg strength.

Mechanism of action:
Ribociclib is an orally bioavailable, highly selective small molecule inhibitor of CDK4/6 that potently induces G1 arrest with sub-micromolar IC50's in a variety of pRb-positive cancer cells.

Storage and stability:
Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].
Ribociclib study medication will be packaged into blisters. The blisters should be opened only at the time of administration, as the drug is hygroscopic and light sensitive. All blisters will conform to all local regulatory requirements.
Storage conditions for ribociclib will be described on the medication label/ local package insert.
The study drug should be stored in a secure, locked area while under the responsibility of the investigator. An authorized person at the investigator's site throughout the entire study must record receipt and dispensing of supplied study drugs.
As long as the study drugs are supplied by Novartis, they are to be stored below 25°C room temperature and protect from moisture. The storage temperature must be recorded weekly in the temperature log.

Route of administration:
p.o.

Manufacturer:
Novartis Pharma GmbH

4.3.2 Contraindications

Hypersensitivity against ribociclib or any CDK 4/6 inhibitor.

4.3.3 Safety

The most frequently reported AEs (≥10%), regardless of grade, causality and ribociclib dose were: nausea (52.3%); fatigue (40.9%); diarrhea (37.1%); vomiting (35.6%); neutropenia (34.1%); anemia (32.6%); decreased appetite, thrombocytopenia (23.5% each); white blood cell count decrease (22.7%); leukopenia (22%); constipation (21.2%); dyspnea (20.5%); asthenia (19.7%); cough (18.2%); hyperglycemia (17.4%); headache, hypoalbuminemia (16.7% each); ECG QT prolonged (15.9%); abdominal pain, back pain, lymphocyte count decrease, pyrexia (15.2% each); AST increase, blood creatinine increased, dizziness, lymphopenia (14.4% each); peripheral edema (13.6%); neutrophil count decreased (12.9%); ALT increase, pain in extremity (12.1% each) and hypocalcemia (11.4%).
QT changes become evident in the first cycle by Day 8 and later (once steady state is reached), are associated with the maximum drug levels between 1 to 8 h post-dose, and remain stable or improve in subsequent cycles.

Please also refer to the most current version of Summary of medicinal Product Characteristics (SmPC) and Investigator's Brochure (IB).

4.3.4 Supply

The IMP Kisqali® (ribociclib**)** is provided by Novartis Pharma GmbH. Novartis Pharma GmbH is responsible for shipment of the IMP **Kisqali®** to the clinical trial centers. **Kisqali®** in combination with **the allowed** endocrine **agents** will be provided by Novartis to the participating sites in the study setting and will be dispensed by the study center personnel on an outpatient basis. Investigator's request of ribociclib will be done through the eCRF (initial order automatically with recruitment, follow up orders as required).

4.3.5 Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of only for study drugs supplied by Novartis in a drug accountability log. The field monitor will note drug accountability during site visits and at the completion of the study. Patients will be asked to return all unused Novartis-supplied study drugs and packaging on an ongoing basis or at the time of study drug discontinuation.

4.4 Combination Chemo- or Endocrine Therapy

Chemo- or endocrine therapy is performed in accordance with the Working Group for Gynecological Oncology (AGO) guidelines and according to the authorized use. The decision for the chemo- or endocrine drugs in individual patients is on the discretion of the investigator.

In the chemotherapy-arm capecitabine (p.o.), docetaxel. (i.v.) paclitaxel (i.v.) vinorelbine (p.o. or i.v), nab-paclitaxel or eribulin may be used in combination with Herceptin® / Perjeta® .

In the endocrine arm aromatase inhibitors, fulvestrant and LHRH analogues may be used in combination with Herceptin® / Perjeta® plus Kisqali® .

For recommended dosing regarding the combination chemo- or endocrine therapies refer to section 5.1, Table 5.

4.4.1 Combination Drug Capecitabine

Pharmaceutical form:
Capecitabine is an orally-administered chemotherapeutic agent and is available as film-coated tablets containing 500 mg Capecitabine.

Mechanism of action:
Capecitabine acts as a prodrug, that is enzymatically converted to the active cytotoxic substance 5-fluorouracil (5-FU) in the body.
5-FU is a fluorinated pyrimidine - analogue antimetabolite. For cytotoxicity, 5-FU requires further intracellular activation to one of several metabolites: Fluorodeoxyuridine monophosphate is a potent inhibitor of thymidilate synthase, an enzyme necessary for the synthesis of dTTP and ultimately DNA. Fluorouridine triphosphate incorporates into RNA and interferes with its processing and function. Fluorodeoxyuridine triphosphate is incorporated into DNA and eventually leads to DNA strand breakage.

Storage and stability:
It should not be stored > 30°C.

Route of administration:
Twice a day p.o. over 14 days, followed by a therapy-free period of 7 days.

Safety:
The most common side effects with cabecitabine as monotherapy are anorexia, diarrhea, nausea, emesis, stomatitis and skin disorders (hand-foot-syndrom).
In combination therapy blood disorders (anemia, leukopenia, neutropenia), disorders of the nervous system (e.g. paresthesia, head ache), oedema, myalgia, arthralgia, pain, indigestion and shortness of breath are added.
Please refer also to the most current version of SmPC.

4.4.2 Combination Drug Docetaxel

Pharmaceutical form:
Docetaxel is available as concentrate for solution for infusion in a vial containing 20 mg drug / ml.

Mechanism of action:
Docetaxel exerts its anti-mitotic activity by binding to microtubules thereby stabilizing microtubules and permitting mitosis of the cell.

Storage and stability:
It should not be stored > 25°C and should be protected from light.

Route of administration:
Docetaxel is administered via a one-hour infusion (i.v.) every three weeks.
Premedication with corticosteroids is recommended before each administration of docetaxel to reduce fluid retention and hypersensitive reactions (e. g. 16 mg Dexamethason given daily over 3 days, starting one day before docetaxel-infusion).

Safety:
The most common hematological side effects of docetaxel are neutropenia and anemia.
Non-hematological adverse effects include alopecia, diarrhea, nausea and stomatitis.
Please refer also to the most current version of SmPC.

4.4.3 Combination Drug Paclitaxel

Pharmaceutical form:
Paclitaxel is available as concentrate for solution for infusion in a vial.

Mechanism of action:
As docetaxel, paclitaxel has anti-mitotic activity. Paclitaxel binds to microtubules, stabilizes the microtubule polymer and permits disassembly thus interfering with the mitosis process in dividing cells.

Storage and stability:
It should be stored < 25°C and protected from light.

Route of administration:
Paclitaxel is administered via a three-hour infusion (i.v.).
Premedication with corticosteroids, antihistamine and H_2- antagonist is recommended.

Safety:
Common non-hematological side effects include nausea and vomiting, loss of appetite, change in taste, thinned or brittle hair, pain in the joints of the arms or legs and changes in the color of the nails.The most common hematological side effects of are neutropenia, anemia, thrombocytopenia, leucopenia and bleeding.Please refer also to the most current version of SmPC.

4.4.4 Combination Drug Vinorelbine

Pharmaceutical form:
Vinorelbine is available as concentrate for solution for infusion in a vial.

Mechanism of action:
Vinorelbine is a spindle inhibitor thereby affecting the mitosis process in dividing cells.

Storage and stability:
Vinorelbine must be stored at 2º- 8º C and has to be protected from light.

Route of administration:
It is administered i.v. as Bolus infusion or in the form of a short infusion (20-30 minutes).

Safety:
Common non-hematological side effects include infections, allergic reactions, alopecia, fatigue, paraesthesia, dyspnea, obstipation, nausea and vomiting.
The most common hematological side effects of are neutropenia, anemia and thrombocytopenia.
Please refer also to the most current version of SmPC.

4.4.5 Combination Drug Nab-Paclitaxel (Abraxane®)

Pharmaceutical form:
Nab-Paclitaxel is supplied as a sterile, lyophilized powder for injectable suspension.

Mechanism of action:
Nab-Paclitaxel has as well as Paclitaxel anti-mitotic activity. Nab-Paclitaxel binds to microtubules, stabilizes the microtubule polymer and permits disassembly thus interfering with the mitosis process in dividing cells. It is a formulation of Paclitaxel bound to albumin nano-particles which enables the reversibly albumin-bound transportation across the endothelial cell in order to concentrate Paclitaxel in areas of tumor.

Storage and stability:
It should be stored < 25ºC and protected from light.

Route of administration:
Nab-Paclitaxel is supplied as a sterile, lyophilized powder for injectable suspension.

Safety:
Common non-hematological side effects include nausea and vomiting, loss of appetite, change in taste, alopezia, pain in the joints of the arms or legs and changes in the color of the nails.
The most common hematological side effects are neutropenia, anemia, thrombocytopenia, leucopenia and bleeding. Please refer to current IB.

Supply:
Abraxane® is provided free of charge by Celgene. The provided study medication will be labelled study-specific and not patient-specific (protocol code: D-V).
Investigator's request of Abraxane® will be made to the central pharmacy through the eCRF (initial order automatically with randomization, follow up orders as required). Manufacturer is Fisher Clinical Services (FCS) Horsham, Steven Pye, Langhurst Wood Road, Horsham RH12 4QD. FCS is responsible for shipment of Abraxane® to the national distributor, which is the Central Pharmacy Klinik-Apotheke, Universitätsklinikum Carl Gustav Carus, Fetscherstr. 74. 01307 Dresden. The central pharmacy distributes Abraxane® to the clinical trial centers.

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. At the end of the trial, all unused trial medication and all medication containers will be destroyed at the pharmacy or 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:
On dispensing study medication to the patient: patient identification number, date, batch number, signature of the responsible staff member.
On obliteration of study medication: Amount, date and signature of the responsible staff member.

Drug accountability is documented in the eCRF.

4.4.6 Combination Drug Eribulin (Halaven®)

Pharmaceutical form:
Eribulin (HALAVEN®) 0.44 mg/ml solution for injection is a clear, colourless aqueous solution. One ml contains eribulin mesilate equivalent to 0.44 mg eribulin. Each 2 ml vial contains eribulin mesilate equivalent to 0.88 mg eribulin. This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose as well as water (for injections), hydrochloric acid (for pH-adjustment) and sodium hydroxide (for pH-adjustment).

Mechanism of action:
Eribulin is a non-taxane, microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. Eribulin inhibits the growth phase of microtubules leading to a G2/M cell-cycle block, disruption of mitotic spindles and, ultimately, apoptotic cell death after prolonged mitotic blockade.

Storage and stability:
This medicinal product does not require any special storage conditions. From a microbiological point of view unless the method of opening precludes the risk of microbial contamination the product should be used immediately. If not used immediately eribulin as the undiluted solution in a syringe should not normally be stored longer than 4 hours at 25°C and ambient lighting, or 24 hours at 2°C - 8°C, in-use storage times and conditions are the responsibility of the user. Diluted solutions of eribulin (0.018 mg/ml to 0.18 mg/ml eribulin in sodium chloride 9 mg/ml (0.9%)) solution for injection should not be stored longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
The storage temperature must be recorded weekly in the temperature log.

Route of administration:
Eribulin is administered i.v. as a ready to use solution over 2 to 5 minutes.

Safety:
Common non-hematological side effects include infections, peripheral neutropenia, dyspnea, nausea, vomiting and loss of appetite.
The most common hematological side effects of are neutropenia, anemia and leukopenia.
Please refer also to the most current version of SmPC.

Supply:
Halaven® is provided free of charge by Eisai if used outside the official EMA label. The provided study medication will be labeled study-specific and not patient-specific. Eisai GmbH is responsible for shipment of eribulin to the clinical trail centers.
Investigator's request of Halaven® will be done through eCRF (initial order automatically with recruitment, follow up orders as required). Manufacturer is Eisai GmbH, Lyonerstr. 36, D-60528 Frankfurt/Main.

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. At the end of the trial, all unused trial medication and all medication containers will be completely returned to Eisai 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 Eisai 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, signature of the responsible staff member.
On obliteration of study medication: Amount, date and signature of the responsible staff member.

Drug accountability is documented in the eCRF.

4.4.7 Combination Drug Exemestane

Pharmaceutical form:
Exemestane is available as film-coated tablets.

Mechanism of action:
Exemestane is an oral steroidal aromatase inhibitor. It is structurally related to the natural substrate androstenedione of the aromatase enzyme. Binding of exemestane to the enzyme it is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation.

Storage and stability:
There are no special storage requirements recommended.

Route of administration:
p.o.

Safety:
The most common non-hematological side effects include loss of appetite, insomnia, head ache, hot flushes, nausea and joint pain.
Hematological side effects occur only occasionally.
Please refer also to the most current version of SmPC.

4.4.8 Combination Drug Letrozole

Pharmaceutical form:
Letrozole is available as film-coated tablets.

Mechanism of action:
Letrozole is an oral non-steroidal aromatase inhibitor. It prevents the aromatase from producing estrogens by competitive, reversible binding.

Storage and stability:
There are no special storage requirements recommended.

Route of administration:
p.o.

Safety:
The most common non-hematological side effects include depression, head ache, hot flushes, sweating, nausea, arthralgia and fatigue.
Hematological side effects occur only occasionally.
Please refer also to the most current version of SmPC.

4.4.9 Combination Drug Anastrozole

Pharmaceutical form:
Anastrozole is available as film-coated tablets.

Mechanism of action:
It is a non-steroidal aromatase-inhibiting drug. It binds reversibly to the aromatase enzyme through competitive inhibition and inhibits the conversion of androgens to estrogens

Storage and stability:
There are no special storage requirements recommended.

Route of administration:
p.o.

Safety:
The most common non-hematological side effects include anorexia, head ache, hot flushes, nausea, arthralgia, fatigue and vaginal bleeding.
Hematological side effects occur only occasionally.
Please refer also to the most current version of SmPC

4.4.10 Combination Drug Fulvestrant

Pharmaceutical form:
Fulvestrant is available as solution for injection in a pre-filled syringe with injection needle.

Mechanism of action:
Fulvestrant is an estrogen receptor antagonist, which works by down-regulating the estrogen receptor.

Storage and stability:
Fulvestrant should be stored protected from light at 2º- 8º C.

Route of administration:
intramuscular injection

Safety:
The most common side effects include infections, allergic reactions, anorexia, head ache, nausea,vomiting, skin rash, asthenia and back pain.
Please refer also to the most current version of SmPC.

4.4.11 Combination Drug LHRH-analogue Goserelin

Pharmaceutical form:
Goserelin is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (12.82-14.76 mg/dose) impregnated with goserelin acetate equivalent to 3.6 mg s.c. of goserelin in a disposable syringe device fitted with a 14-gauge x 36 +/- 0.5 mm siliconized hypodermic needle with protective sleeve.

Mechanism of action:
Goserelin is a synthetic decapeptide analogue of LHRH and acts as a potent inhibitor of pituitary gonadotropin secretion.

Storage and stability:
Goserelin should be stored at room temperature .

Route of administration:
Subcutaneous injection

Safety:
The most common side effects include hot flashes, pain (general, gynecomastia, pelvic pain, bone pain, asthenia.

4.4.12 Combination Drug LHRH-analogue Leuprorelin

Pharmaceutical form:
Leuprolide is supplied in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a 3,75 mg/ 11,25 mg leuprolide suspension intended as a monthly/three monthly s.c. injection.

Mechanism of action:
Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses.

Storage and stability:
Leuprolide should be stored Store below 77°F (25°C). Do not freeze. Protect from light; store vial in carton until use.

Route of administration:
One month depot: Subcutaneous injection. Three month depot: subcutaneous injection.

Safety:

The most common side effects include redness/burning/stinging/pain/bruising at the injection site, hot flashes (flushing), increased sweating, night sweats, tiredness, headache, upset, stomach, nausea, diarrhea, constipation, stomach pain, breast swelling or tenderness, acne, joint/muscle aches or pain.

5 Treatment Plan

5.1 Treatment Regimen

Study Design and Plan Protocol Version 1.1 03.06.2015

Patients will be treated with Herceptin® (Trastuzumab) / Perjeta® (Pertuzumab) and chemotherapy or endocrine therapy according to randomization.

A switch from combination chemotherapy to endocrine therapy or vice versa is not allowed.

Herceptin® / Perjeta® have to be administered as intravenous infusions prior to chemotherapy. The sequence of administration of Herceptin® and Perjeta® is not specified.
After each infusion of pertuzumab an observation period of 30 – 60 minutes is recommended prior to subsequent infusion of chemotherapy.

With the amendment coming into effect, the CDK4/6 inhibitor Kisqualí® (ribociclib) will be added to both therapy arms:

Arm A: endocrine-based therapy arm:

Patients will be treated with Herceptin® (Trastuzumab) / Perjeta® (Pertuzumab) plus ribociclib with standard endocrine therapy until progression or inacceptable toxicity.

A switch from one endocrine to another endocrine agent due to intolerability is not allowed.
After discontinuation of endocrine therapy due to inacceptable toxicity treatment with Perjeta® and Herceptin® and ribociclib should be continued till progress or inacceptable toxicities.

After discontinuation of Ribociclib due to inacceptable toxicity treatment with Perjeta® (420 mg d1 q3w) and Herceptin® (6 mg/kg body weight, d1 q3w) in combination with endocrine therapy should be continued till progress or inacceptable toxicities.

Treatment with either Herceptin® or Perjeta® alone is not allowed. Ribociclib in combination with trastuzumab and pertuzumab without endocrine therapy is allowed if endorcrine treatment is not tolerated.

Arm B or Chemotherapy arm:

Patients will be treated with Herceptin® (Trastuzumab) / Perjeta® (Pertuzumab) in combination with monochemotherapy according to the allowed regimens. Duration of chemotherapy must be at least 4 months unless there is progression of the disease or inacceptable toxicity.

After completion of chemotherapy patients will be treated with maintenance Herceptin® (Trastuzumab) / Perjeta® (Pertuzumab) and endocrine therapy in combination with ribociclib. It is allowed to start with endocrine therapy up to 3 weeks after completion of chemotherapy and ribociclib up to 6 weeks after completion of chemotherapy.

After discontinuation of ribociclib due to inacceptable toxicity treatment with Perjeta® and Herceptin® in combination with endocrine therapy should be continued till progress or inacceptable toxicities.

Treatment with either Herceptin® or Perjeta® pertuzumab alone is not allowed.

Ribociclib in combination with trastuzumab and pertuzumab without endocrine therapy is allowed.

A switch from chemotherapy to endocrine-based therapy or vice versa is not allowed.

Recommended dosing:

- **Perjeta® (*Pertuzumab):***

Initial dosing: 840 mg Perjeta® as intravenous infusion over 60 minutes, d1.
For subsequent infusions: 420 mg Perjeta® as intravenous infusion over 30-60 minutes, q3w.

- **Herceptin® (*Trastuzumab):***

Initial dosing: 8 mg/kg body weight Herceptin® as intravenous infusion over 60-90 minutes, d1. For subsequent infusions: 6 mg/kg body weight Herceptin® as intravenous infusion over 30 minutes, q3w.

For recommendations regarding delayed or missed doses please refer to the currently valid SmPC.

- **Kisqali ® (Ribociclib):**

On treatment Day 1, patients will be provided study drugs for self-administration at home. Enough tablets should be provided or prescribed to cover administration until next scheduled visit plus one week at minimum.
Patients will take ribociclib capsules orally per day (3-weeks-on/1-week-off schedule) and will also take standard endocrine therapy once daily (dosage according to the label).
Patients should be instructed to take the study drug combination of ribociclib and standard endocrine therapy with a large glass of water (~250 mL) at the same time each day. Evening doses are strongly not recommended.

Ribociclib can be admistered with or without food; however dietary habits aroud the time of dosing should be as consistent as possible throughout the study.

Patients should be instructed to swallow the ribociclib whole and not to chew or crush them.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next schedule dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section in the eCRF.

Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on subsequent day.

Patients must avoid consumption of grapefruit, grapefruit hybrids, pummelos, starfruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications.
Note: Orange juice is allowed.

- No herbal or dietary supplements are permitted.
- Multivitamins are permitted.

The investigator should promote compliance by instructing the patient to take the study drugs exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if she is unable for any reason to take the study drug as prescribed.

Endocrine therapy:

Exemestane / letrozole / anastrozole / fulvestrant / LHRH analogues will be dosed starting on treatment Day 1 according to the recommended daily dosage (refer to table 7). Package insert instructions should be followed.

Chemotherapy:
Substances for chemotherapy may be either cabecitabine, docetaxel, eribulin, paclitaxel, nab-Paclitaxel or vinorelbine (i.v./p.o.) according to the investigator's choice
For endocrine therapy either Aromatase Inhibitors or Fulvestrant may be used according to the investigator's choice. LHRH analogs will be given in combination with AI in pre- and perimenopausal women. For dosing please refer to table 7.

Chemotherapy	**Recommended Dosing**
Docetaxel	75 mg/m^2 i.v. d1 q3w
Paclitaxel	Two regimens are available: 90 mg/m^2 i.v. d1, 8, 15 q4w or 80 mg/m^2 i.v. d1, 8, 15, 22 q4w; duration of the treatment with paclitaxel is at the discretion of the investigator, at least 4 months or until disease progression or inacceptable toxicity)
Capecitabine	2 x 1000 mg/m^2 p.o. d1-14 q3w; duration of the treatment with capecitabine is at the discretion of the investigator
Vinorelbine	30 mg/m^2 i.v..* d1+d8 q3w; duration of the treatment with vinorelbine is at the discretion of the investigator (at least 4 months or until disease progression or inacceptable toxicity)
Nab-Paclitaxel	125 mg/m² d1, 8, 15 q4w; duration of the treatment with nab-paclitaxel is at the discretion of the investigator (at least 4 months or until disease progression or inacceptable toxicity)
Eribulin	1,23 mg/m² i.v. d1, 8 q3w; duration of the treatment with eribulin is at the discretion of the investigator (at least 4 months or until disease progression or inacceptable toxicity)
Endocrine therapy	**Recommended Dosing**
Exemestane	25 mg/d p.o.
Letrozole	2,5 mg/d p.o.
Anastrozole	1 mg/d p.o.
Fulvestrant	500 mg i.m. d1+15+28, then 500 mg i.m. q28d
Leuprorelin	3,75 mg 1 M Depot s.c. q4w, 11,25 mg 3 M Depot s.c.
Goserelin	3,6 mg s.c. q4w

Table 7: Recommended dosing for combination chemo- or endocrine therapy

5.2 Planned Treatment Duration per Subject

Duration of chemotherapy must be at least 4 months unless there is progression of the disease or inacceptable toxicity. After discontinuation/completion of chemotherapy, maintenance treatment with Perjeta® (420 mg d1 q3w) and Herceptin® (initial 8 mg/kg, further infusions with 6 mg/kg body weight, d1 q3w) in combination with ribociclib plus standard endocrine therapy will be given till progress or inacceptable toxicities.

After discontinuation of endocrine therapy due to inacceptable toxicity treatment with Perjeta® and Herceptin® and ribocciclib should be continued till progress or inacceptable toxicities.

After discontinuation of Kisqali® due to inacceptable toxicity treatment with Perjeta® and Herceptin® in combination with endocrine therapy should be continued till progress or inacceptable toxicities.

5.3 Removal of Subjects from Study

Each patient remains in the study until either the patient or the investigator determines discontinuation to patient's best interest.

Patients who discontinue participation in the clinical study on their own by withdrawal of informed consent (at any time) or patients who are withdrawn by the investigator, for reasons other than disease progression, will be defined as premature withdrawals.

5.4 Protocol Treatment Discontinuation

Criteria for discontinuing standard chemo- or endocrine therapy:

- Tumor progression (as defined in section 8.4)
- Inacceptable toxicity
- Pregnancy
- Request by the patient
- For medical and any other reasons considered relevant by the physician

Criteria for discontinuing Kisqali® treatment:

- Tumor progression (as defined in section 8.4)
- Inacceptable toxicity
- Pregnancy
- Request by the patient
- For medical and any other reasons considered relevant by the physician

Criteria for discontinuing Herceptin® + Perjeta® treatment:

- Tumor progression (as defined in section 8.4)
- Inacceptable toxicity
- Pregnancy
- Request by the patient
- For medical and any other reasons considered relevant by the physician

Note:
In patients with first new parenchymal CNS metastases appearing under trial treatment, well controlled by radiotherapy (no new cerebral lesions or no PD of the present cerebral), but no PD of the lesions outside the CNS, trial treatment should be continued until progression at one of the extra-cerebral lesions or at the irradiated CNS metastases occurs. Therefore, first new parenchymal CNS metastases only do not count for PD requiring the initiation of second line trial treatment. Any meningeosis counts for PD.

5.5 Duration of Protocol Treatment

Duration of study treatment:

- depends on the agents and dose regimes chosen

- depends on the occurrence of tumor progression, inacceptable toxicity or other criteria for discontinuation
- chemotherapy treatment duration should not be less than 4 months (unless earlier treatment discontinuation is medically indicated)
- is limited to the 12 month study treatment period, but all therapies can be extended beyond the end of the study treatment period if medically indicated. The investigators are encouraged to proceed with the given treatment unless there is inacceptable toxicity or progression. CT examinations are recommended every 9-12 weeks. If progression of disease is suspected immediate radiological examination is recommended.

5.6 Therapy after End of Protocol Treatment

- Therapy during the follow-up period for patients is at the discretion of the investigator. All therapies given in the study treatment period can be extended if medically indicated and , but study medication is only provided until the end of the follow-up period. The investigators are encouraged to proceed with the given treatment unless there is inacceptable toxicity or progression. CT examinations are recommended every 9-12 weeks. If progression of disease is suspected immediate radiological examination is recommended.

5.7 Premature Termination of Study Participation in Single Patients

Study participation is terminated prematurely with single patients

- Request by the patient
- 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

5.8 Withdrawal from the Study

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The investigator may also, at his/her discretion, withdraw the subject from participating in this study at any time, or the sponsor may discontinue the study.

Reasons for early withdrawal from the study should be documented in the eCRF as:

- Study closed/terminated
- Subject lost to follow-up
- Investigator’s decision
- Subject withdrew consent

Date of withdrawal from the study, with reason for withdrawal, will be documented in the subject's medical record and recorded on the eCRF. In the case of death, a death certificate should be obtained if possible, with the cause of death evaluated and documented.

5.9 Study Discontinuation

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

Study discontinuation is at the discretion of the sponsor in any of the following events:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects

In addition, the study may be discontinued at the discretion of the sponsor in the event of any or all of the following:

- Inefficacy of the investigational product
- Occurrence of AEs previously unknown in respect of their nature, severity and duration, or unexpected incidence of known AEs

Safety data from the study will be reviewed by the sponsor on a regular and ongoing basis in order to ensure the safety of the patients.

5.10 Definition of the End of Study

The end of study is defined as the last visit of the last patient in the follow-up-period. Phone contact during the follow-up-period will not be regarded as a visit.

5.11 Plan for Treatment after the End of Study Therapy

Following the end of treatment evaluation (= 28 days after d1 of the last administration of study medication) or the end of treatment for any other cause, patients will be treated and followed according to the guidelines of the German Cancer Society.

6 Adaption

6.1 General Notes Regarding Dose Modifications for Therapy-Related Toxicity

Dose modifications of Perjeta® or Herceptin® are not allowed. Treatment with Herceptin® and Perjeta® can be continued in case of reversible myelosuppression induced by chemotherapy. During this time patients have to be monitored very close for neutropenia.
In case of discontinuation of endocrine therapy due to toxicities treatment with Herceptin®and Perjeta® can be continued.
In case of inacceptable toxicities due to either Herceptin® or Perjeta®, administration of both drugs has to be discontinued.

6.2 Dose Modification and Treatment Alteration due to adverse events

Herceptin® and Perjeta®:

No dose modifications are allowed.

In case of ≥ 10% reduction of the initial value of the left ventricular ejection fraction (LVEF) and LVEF < 50% the treatment should be interrupted. Within 3 weeks a new LVEF measurement should be performed. In case of no changes or further deterioration treatment with Herceptin® and Perjeta® should be terminated.

The management of Pertuzumab/Trastuzumab for patients who have an asymptomatic decrease in LVEF is shown in Figure 5:

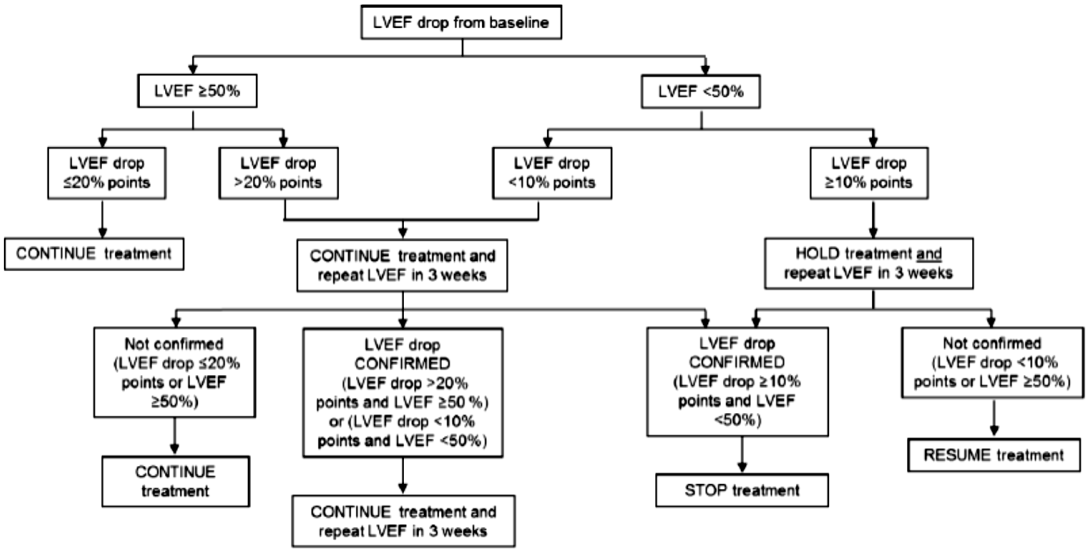


Figure 5: Asymptomatic decrease in LVEF: Algorithm for continuation and discontinuation of pertuzuman/trastuzumab

Kisqali®:

For patients who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions are permitted in order to keep the patient on the study drugs. The following guidelines should be followed.

These changes must be recorded on the Dosage Administration Record eCRF.

Treatment with ribociclib and standard endocrine therapy should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Management of severe and/or intolerable suspected adverse events may require temporary dose reduction and/or interruption.

For patients who do not tolerate the protocol-specified ribociclib dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study. The following guidelines need to be applied:

All study drug interruptions or dose modifications must be recorded on the Dosage Administration Record page of the eCRF.

	Dose	Number of tablets & strength
Starting dose	600 mg/d	3 x 200 mg tablets
First Dose reduction	400 mg/d	2 x 200 mg tablets
Second dose reduction	200 mg/d	1 x 200 mg tablets

Table 8: Ribociclib Dose Modification guidelines

If a patient has already decreased ribociclib intake to 200 mg every other day, no further dose reduction is permitted. Patients requiring an additional ribociclib dose reduction will be required to discontinue study treatment.

Patients who interrupt ribociclib therapy for more than 6 weeks must discontinue the ribociclib therapy, therapy with Trastuzumab and Pertuzumab can be continued.

Table 9 and Table 10 provide the procedure to be followed for ribociclib dose modification in the event of toxicities suspected to be related to the ribociclib treatment. Included are also instructions for re-initiation of ribociclib dosing once sufficient recovery of toxicity is seen.

Toxicity	Actions
Thrombocytopenia **Platelet count**	• **Grade 1 (≥ 75 x 10^9):** No change • **Grade 2 (50 x 10^9 – 75 x 10^9)** Dose interruption until recovery to grade ≤ 1 Reintroduce ribociclib at the same dose level • **Grade 3 (25 x 10^9 – 50 x 10^9)** Dose interruption until recovery to grade ≤ 1 Reintroduce ribociclib at the same dose level If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤ 1 and reduce ribociclib to the next lowev dose level. • **Grade 4 (<25 x 10^9)** Dose interruption until recovery to grade ≤ 1 Reintroduce ribociclib at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib.
Absolute Neutrophil count (ANC)	• **Grade 1 (≥ 1,5 x 10^9)**: No change • **Grade 2 (1,5 x 10^9 - 10^9)**: No change • **Grade 3 (0,5 x 10^9 - 10^9)**: Dose interruption until recovery to ⩾ 1.0 x 10^9/L Reindroduce ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to ≥ 1.0 x 10^9/L If resolved in ≤ 7 days, then maintain dose level. If resolved in > 7 days, then reduce ribociclib dose to the next lower dose level. • **Grade 4 (<0,5 x 10^9)**: Dose interruption until recovery to ≥ 1.0 x 10^9/L Reindroduce ribociclib at the next lower dose level. If toxicity recurs at grade 4: temporary dose interruption until recovery to ≥ 1.0 x 10^9/L And reduce ribociclib at the next lower dose level.
Febrile neutropenia	• **Grade 3 (ANC < 1.0 x 10^9/L with a single temperature of > 38.3˚ C or a sustained temperature of ≥ 38˚ for more than one hour)**: Dose interruption until improvement of ANC ≥ 1.0 x 10^9/L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib. • **Grade 4 (Life-threatening consequences; urgent intervention indicated):** Discontinue ribociclib.
Anemia (Hemoglobin)	• **Grade 1 (⩾ 10.0 x LLN g/dl)**: No change • **Grade 2 (≥ 8.0 - < 10 x LLN g/dl)**: No change • **Grade 3 (< 8.0 x LLN g/dl)**: Dose interruption until recovery to grade ≤ 2. Reintroduce ribociclib at the same dose. • **Grade 4 (Life-threatening consequences; urgent intervention indicated):** Discontinue ribociclib

Physicians should always manage patients according to their medical judgment based on the particular clinical circumstances.

Table 9: Ribociclib dose adjustment and management recommendations for hematological adverse reactions

Toxicity	Actions
HEPATOTOXICITY (BILIRUBIN; SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	**Grade 1 (> ULN-2.0 x ULN) :** Maintain dose level with LFTs monitored bi-weekly **Grade 2 (> 2.0 ULN - 3.0 x ULN):** Dose interruption of ribociclib If resolved to ⩽ grade 1 in ≤ 21 days, then maintain dose level If resolved to ≤ grade 1 in > 21 day or toxicity recurs, then reduce 1 dose level Repeat liver enzymes and bilirubin tests twice weekly for two weeks after dose resumption If toxicity recurs after two dose reductions, discontinue ribociclib **Grade 3 (> 3.0 ULN -10.0 x ULN)::** Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤ 21 days, lower 1 dose level of ribociclib Repeat liver enzymes and bilirubin tests twice weekly for two weeks after dose resump tion If resolved to ≤ grade 1 in > 21 days or toxicit recurs, discontinue ribociclib treatment **Grade 4 (> 10.0 ULN):** Discontinue ribociclib treatment
Confounding factors and/or alternative causes for increase of total bilitubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia de to the indirect component (i.e. direct bilirubin component ≤ 1x ULN) due to hemolysis or Gilbert Syndrome, pharmocologic treatment, viral hepatitis, alcoholic or autoimmune hepatits, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to change in direct bilirubin only. Bilirubin will be fractionated if elevated.	
AST or ALT without bilirubin elevation > 2 x ULN	**Same grade as baseline or increase from baseline grade o to grade 1 (confirmed 48-72 h later) :** No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1. **Increase from baseline 0 or 1 to grade 2 (> 3.0 – 5.0 x ULN):** Dose interruption of ribociclib If resolved to ≤ baseline grade in ≤ 21 days or toxicity recurs, then reduce 1 dose level Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is > 28 days, discontinue ribociclib **Increase from baseline 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN):** Dose interruption of ribociclib until resolved to ≤ baseline until resolved to ≤ basline grade, then lower 1 dose level of ribociclib Repeat liver enzyme ans bilitubin tests twice weekly for two weeks after dose resumption If recovery to ≤ baseline grade > 28 days, discontinue ribociclib If toxicity recurs, discontinue ribociclib **Increase from baseline from grade 2 to grade 3 (> 5.0 – 20.0 x ULN):** Dose interruption of ribociclib until resolved to ≤ baseline grde, than lower 1 dose lever of ribociclib Repeat liver enzyme ans bilirubin tests twice weekly for two wetoeks after dose resumption If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is > 28 days, discontinue **Grade 4 (> 20.0 x ULN):** Discontinue ribociclib

AST or ALT and concurrent Bilirubin	**For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT > 3.0 ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis** **OR** **For patients with elevated AST or ALT or total bilirubin at baseline: baseline: (AST or ALT > 2 x baseline AND > 3.0 x ULN) OR (AST or ALT 8.0 x ULN) – whichever is lower - -combined with (total bilirubin > 2 x baseline AND ≥ 2.0 ULN)** Discontinue ribociclib treatment

Cinfounding factors and /or altenative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastases, and alcohol intake

Table 10: Ribociclib dose adjustment and management recommendation for hepatic toxicities

Additional follow up for QTc prolongation

For All Grades	• Check the quality of the ECG and the QT value and repeat if it needed • Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. • Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. • Check compliance with correct dose and administration of ribociclib. • Consider collecting a time matched PK sample; record date and time of last study drug intake
1* QTc 450-480 ms	No change
2* QTc 481-500 ms	Interrupt ribociclib. Perform a repeat ECG within one hour of the first QTcF of ≥ 481 ms. If QTcF < 481 ms, restart ribociclib at the same dose. No dose adjustment required for first occurrence. If QTcF remains ≥ 481 ms, repeat ECG as clinically indicated until the QTcF returns to < 481 ms. restart ribociclib at the same dose. No dose adjustment required for first occurrence. If QTcF ≥ 481 ms recurs, ribociclib should be reduced by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms
3 QTc ≥ 501 ms on at least two separate ECGs	Interrupt ribociclib. Transmit ECG immediately and confirm prolongation/abnormalities. Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms. If QTcF returns to < 481 ms, ribociclib will be reduced by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms If QTcF of ⩾ 501 ms recurs, discontinue ribociclib.
4* [QT/QTc ≥ 501 or > 60 ms change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia]	Discontinue ribociclib. • Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.

*All values refer to the average of triplicate measurements

Table 11: Ribociclib dose adjustment and management recommendation for all other adverse reactions

Guidance for all other adverse reactions:

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions, if indicated. If electrolyte values are outside of the normal range, interrupt ribociclib administration, correct electrolytes with supplements or appropriate therapyas soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

Patients who experience renal impairment (not due to other contributing factors) of grade 2 or higher during the treatment period should discontinue treatment and should be followed for safety assessments.

For all other adverse events please follow recommendations in table 12

Grade	Ribociclib dose adjustment and management recommendation
1	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
2	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the same dose. If the same toxicity recurs at grade 2, interrupt ribociclib until recovery to grade ≤1. Re-initiate ribociclib at the next lower dose level.
3	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce ribociclib dose the next lower dose level. If toxicity recurs at grade 3, discontinue ribociclib.
4	Discontinue ribociclib and treat with appropriate medical therapy.

Table 12: Ribociclib dose adjustment and management recommendation for all other adverse reactions

Chemotherapy:

In case of severe/inacceptable toxicities dose modifications and treatment alterations may be performed according to national / international guidelines as well as recommendations in summary of medicinal product characteristics (SMPC) and/or investigators broschure.

Dose modifications should consider the organ system showing the greatest degree of toxicity. Note that the doses which have been reduced for toxicity reasons must not be re-escalated (except for liver function tests if improved to within ranges given).
If necessary Nab-paclitaxel should be reduced to 100 mg/m²or 80 mg/m² as first / second step.

Endocrine therapy:

Therapy with endocrine drugs may be interrupted for up to 4 weeks due to toxicities.

7 Concomitant therapy

In the eCRF the use of all drugs, over-the-counter medications, or alternative therapies including herbal supplements, taken by the patient in the period from 2 weeks prior to randomization till the last Follow up assessment will be captured.

7.1 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 clinical trial, including transfusion of blood products, and treatment with growth factors, antibiotics, antiemetics, antidiarrheals and analgesics when clinically indicated and according to the the center's standard practice, with the exception of the therapies mentioned in section 7.2.

  All supportive treatments have to be documented in the eCRF.

7.2 Not Permitted

- Anti-cancer treatment other than protocol therapy must not be given until disease progression.
- Primary prophylaxis with G-CSF if therapy with docetaxel is applied.

7.3 Palliative radiotherapy

Palliative radiation 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 Clinical Examinations

8.1 Clinical Examinations prior to Therapy (Screening / Baseline)

The following baseline examinations should be performed within 28 days before start of randomization:

- Informed Consent
- Demographic data, medical history
- CT- or MRI-scan of abdomen, chest and pelvis to document baseline tumor status, TNM staging
- Physical Examination comprising: general appearance, skin, head/neck, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, musculoskeletal and nervous system, extremities, eyes, ears, nose and throat
- Vital signs: body temperature, heart rate, blood pressure, height and weight
- Standard 12- lead ECG
- ECOG performance status assessment
- Hematological and biochemical laboratory assessment including hemoglobin, absolute neutrophil count, leucocytes, platelets, Bilirubin, Creatinine, AST, ALT, (GGT, AP, LDH INR, sodium, potassium, phosphorus, total calcium for ribociclib treatment)
- Blood sample for CTC analysis
- Females of childbearing potential: pregnancy test (serum β-HCG test)

  Female patients of childbearing potential must be informed that they are obliged to practice medically accepted contraception throughout the study and 7 months after date of the last study treatment .

- Quality of life (EORTC-QLQ C30 + BR23)

8.2 Clinical Examinations during Treatment Phase (every 3 weeks)

Prior to every cycle (within 24 hours prior to administration):

- Performance status according to ECOG-Criteria
- Physical and vital signs assessments, as at baseline
- ECG must be performed on d15 of cycle 1, d1 of cycle 2, of **ribociclib treatment**, and as clinically indicated (for patients with QTcF ≥ 481 ms at any time prior to cycle 7: all other cycles on day 1 pre-dose; 9 and every 3rd cycle on day 1 pre-dose and 2 h post dose)
- Hematological and biochemical laboratory assessment as at baseline
- Blood sample for CTC analysis (week 6 after randomization only)
- Survey of concomitant medication
- Adverse events are recorded after every cycle according to NCI-CTCAE-Criteria Version 4.03. Serious adverse events have to be reported within 24 h to the coordinating investigator (section 5.3) on an extra form.

8.3 Clinical Examinations during Treatment Phase (every 9 weeks)

- Tumor assessment using CT- or MRI-Scan and classification of the response according to RECISTv1.1-Criteria.

  If progression of disease is suspected for any reason at or between the 9-weekly evaluation visits, radiological confirmation is necessary and a new scan must be performed unless a scan taken no more than 14 days earlier is available.
- LVEF including ECHO
- Females of childbearing potential: pregnancy test (any positive urine pregnancy test must be confirmed via a serum β-HCG test)
- Quality of life (EORTC-QLQ C30 + BR23)

8.4 Final examinations after the treatment phase (End of treatment evaluation visit)

Final examinations should be performed **28 days** after date of last given study medication according to protocol.

- Adverse events are recorded according to NCI-CTCAE-Criteria and up to 90 days after last administration. Serious adverse events have to be reported within 24 h to the coordinating investigator on an extra form
- Performance status according to ECOG-Criteria
- Physical and vital signs assessments, as at baseline
- Hematological and biochemical laboratory assessment according to baseline
- Tumor assessment using CT- or MRI-Scan and classification of the response according to RECISTv1.1-Criteria.
- Survey of concomitant medication

- Pregnancy test (for premenopausal women)
- Blood sample for CTC analysis (if the protocol treatment has to be discontinued because of tumor progression before the end of the regular 12-month study treatment period, blood sample for CTC analysis will be collected at the time of progression)
- Quality of life (EORTC-QLQ C30 + BR23)

8.5 Examinations during Follow-up Period

The follow-up period will last for 2 years. The following examinations will be performed every 3 months after last treatment administration:

- Survival status
- Adverse events: Final documentation of outcome of adverse events still ongoing at the End of Treatment Evaluation visit.
- Pregnancy test (for premenopausal women)
- Quality of life (EORTC-QLQ C30 + BR23)

9 Translational Research

The main focus of the translational research program in the DETECT V/CHEVENDO study is on investigating the association of presence and molecular characteristics of circulating tumor cells (CTCs) with treatment response and prognosis. Tumor cell dissemination is a crucial step in tumor progression, and blood-derived metastases account for the majority of breast cancer-related deaths. Cells that are able to disseminate into the circulation are of biologic relevance as potential founder cells for new metastases, and CTC detection and characterization have already improved our understanding of the complex process underlying tumor cell dissemination and metastatic progression in breast cancer.

Previous research has shown that CTCs (≥ 1 / 7.5 ml blood) are present in 65-85% of patients with MBC (Fehm et al. 2010, Botteri et al. 2010, Müller et al. 2012, Pierga et al. 2012), and five or more CTCs are detected in about 40-50% of MBC patients (Cristofanilli et al. 2004, Budd et al. 2006, Fehm et al. 2010, Müller et al. 2012, Pierga et al. 2012, Bidard et al. 2014). There is good evidence that CTCs detected in the peripheral blood of patients with MBC can both provide prognostic information (Budd et al. 2006, Cristofanilli et al. 2005, Hayes et al. 2006, Giuliano et al. 2011, Giordano et al. 2012, Wallwiener et al. 2013, Bidard et al. 2014) and indicate therapy success (Liu et al. 2009, Pierga et al. 2012).

Within the DETECT V/CHEVENDO trial, prevalence and number of CTCs in the peripheral blood will be determined parallel to tumor evaluation at baseline (i.e. before the start of treatment), 6 weeks after randomization, and after the 12-month study treatment period or at the time of progression, whatever comes first (if possible in correlation with Re-Staging, e.g. CT-Scan). The FDA approved standardized and semi-automatic CellSearch™ system (Janssen Diagnostics, LLC, Raritan USA) will be used for capture, isolation and enumeration of CTCs. The method has been described in detail in a validation study by Riethdorf et al. 2007, and is now routinely being used in the laboratories responsible for conducting the translational research program in the DETECT V/CHEVENDO study. Briefly, blood samples are collected into special CellSave tubes, centrifuged to separate solid blood components from plasma, and then placed in the CellTracks® AutoPrep® System. Using ferrofluid nanoparticles with antibodies that target epithelial cell adhesion molecule (anti-EpCAM), CTCs are magnetically separated from the other cells in the blood. CTCs are then stained with the fluorescent nucleic acid dye 4',6-diamidino-2-phenylindole (DAPI), cytokeratin monoclonal

antibodies (specific to epithelial cells) and a monoclonal antibody to identify CD45 (a marker specific to leukocytes) to be able to distinguish epithelial cells from leukocytes. A cartridge containing stained CTCs is then automatically placed into the CellTracks Analyzer II®, which generates images of the stained tumor cell candidates (i.e. nucleated cells lacking CD45 and expressing cytokeratin) that are presented to an operator for final review.

In addition to the quantitative assessment of CTCs, the expression of the markers estrogen receptor (ER) and HER2 on isolated CTCs will be determined using the CellSearch® system (as described by Paoletti et al. 2011). Based on the level of expression for these markers and the proportion of CTCs showing such marker expression, an endocrine responsiveness score (ERS) will be calculated and its predictive value for assessing therapy efficacy will be determined. The generation of an ERS is based on the idea that high expression levels of ER are predictive of responsiveness to endocrine therapy, while high HER2- expression levels are indicative of resistance to endocrine therapy. The aim of this project is to create an ERS that allows to predict the responsiveness of patients with hormone-receptor positive and HER2-positive metastatic breast cancer to a combined endocrine and HER2-targeted therapy.

Modified or additional translational research projects to identify or evaluate markers of interest in breast cancer research may be performed.

Blood samples will be collected from patients who consent to participate in translational research at the beginning and 6 weeks after the beginning of study treatment. If a patient objects to blood sampling for this purpose, she may nevertheless participate in the study.

10 Criteria for Tumor Assessment and Response

10.1 Eligibility for Evaluation

Patients with a measurable disease according to RECISTv1.1 criteria before the start of study treatment are eligible for response evaluation according to RECISTv1.1 criteria (Eisenhauer et al. 2009).
Note: The method of tumor response evaluation must not be changed during the course of the study! In case of missing legitimate indication for CT scan, MRI should be performed.

10.2 Criteria for Measurable and Non-Measurable Lesions

Measurable lesions are lesions that can be accurately measured in at least one dimension with longest diameter at least 20 mm using chest X-ray or at least 10 mm with CT scan, MRI techniques or spiral CT scan.
Non-measurable lesions are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm), and any of the following bone lesions, ascites, pleural effusion, cysts and abdominal masses that are not confirmed by imaging techniques.
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (in other words the lesions with the longest diameter) and their suitability for accurate repeated measurements. A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum of the longest diameter. This will be used as reference by which to characterize the objective tumor. All other lesions should be identified as non-target lesions and are not measured at baseline but presence should be noted.

10.3 Definition of Measurable Lesion Response Using RECIST Criteria Version 1.1

Target lesions will be measured in a dimension using the longest diameter is used. The same investigational method must be used throughout.
Complete response (CR): Disappearance of all lesions and appearance of no new lesions.
Partial response (PR): At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum diameters. No new lesions may occur or individual lesions progress.
Progressive disease (PD): At least a 20% increase in the total of the longest diameters of target lesions, taking as reference the smallest sum on study since the treatment started (this includes the baseline sum if that is the smallest on study) or the appearance of new lesions.
If the marker lesion disappears and the progression of a lesion or the appearance of new lesions is observed elsewhere at the same time, this is also documented as a progressive disease.
Stable disease (SD): Neither a partial nor a complete response in the absence of progression.

10.4 Definition of Non-Measurable Lesion Response Using RECIST Criteria Version 1.1

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.

10.5 Best Overall Response According to RECIST Criteria

Target lesions	Non-target lesions	New lesions	Overall response
CR	**CR**	**No**	**CR**
CR	**SD**	**No**	**PR**
PR	**SD**	**No**	**PR**
SD	**SD**	**No**	**SD**
PD	**any**	**Yes or No**	**PD**
any	**PD**	**Yes or No**	**PD**
any	**any**	**Yes**	**PD**

11 Assessment of Safety

Toxicities will be defined according to the NCI-CTCAE-Toxicity Criteria version 4.03 (Appendix 19.1).

11.1 Adverse Events

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 unfavourable 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), that are felt to be clinically significant in the medical and scientific judgment of the investigator, that are associated with symptoms, or that lead to a change in study treatment or concomitant treatment or discontinuation from study drug. This also includes deterioration in pre-existing diseases or events, diseases that occur in the intervening period, changes of medication or a significant deterioration in the disease studied. Furthermore, this includes adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., invasive procedures that occur during screening, such as biopsies etc.). Expected daily variations in the disease under study that do not represent a clinically significant deterioration should not be considered an adverse event.
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.

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”

- Intensity (grade 1 to 5 according to the NCI Common Terminology Criteria for Adverse events (CTCAE) version 4.03),
  If an NCI-CTC classification is not applicable, the side effect must be described on the basis of the following classification:
  Grade 0 = no toxicity
  Grade 1 = mild toxicity; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  Grade 2 = moderate toxicity; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
  Grade 3 = severe toxicity; Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
  Grade 4 = life-threatening toxicity; Life-threatening consequences; urgent intervention indicated.
  Grade 5 = Death related to AE

- 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),

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.

Adverse reactions are all untoward and unintended responses to a medicinal product related to any dose administered.

All expected Adverse Reactions are listed in the Investigator's Brochure (IB) for an unapproved investigational medicinal product or in the Summary of Product Characteristics (SmPC) for an authorized product. If the nature or the severity of an adverse reaction is not consistent with the applicable product information, the adverse reaction is defined as unexpected. The base for the decision is the current version of the corresponding reference document that has been submitted and approved by the competent authority and the ethics committees.

11.2 Follow-Up Examination in the Case of Adverse Events

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

After the safety observation period, the investigator shall report to the sponsor only serious adverse events that are related to the study medication.

11.3 Causal Assessment

The investigator should make every effort to elucidate any adverse event and where necessary to assess its relationship to the study medication.

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, and indicate "yes" or "no" accordingly.

The degree of certainty of the relationship between adverse event and drug is determined by how well the event can be explained by the following factors: (1) known pharmacological properties, (2) comparable reactions observed previously with the drug or another member of its class, (3) an event with comparable substances commonly described in the literature as drug-related, (4) a chronological relationship between the event and drug intake, disappearance on withdrawal or recurrence on re-institution of the drug.

11.4 Definition of Serious Adverse Events

A serious adverse event (SAE) is

- any event that results in death or is life-threatening (an adverse event is life-threatening if the patient's life was in immediate danger, i.e. this does not involve reactions that would only have resulted in death if they had been more serious)
- any event that results in disability or incapacity (i.e. if it significantly and/or persistently impairs the ability of the patient to go about her daily life normally)
- any event that requires hospitalization or results in prolongation of existing hospitalization
- any event that represents a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above)
- any congenital anomaly or birth defect in a neonate or infant born to a mother exposed to study drug

Exceptions

Within this study, the following serious events will be excluded from compulsory notification.

- For the purpose of SAE reporting, hematological adverse events not associated with secondary manifestations – fever, infection or bleeding – are not considered significant medical events with regards to seriousness.
- After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.
- Hospitalization associated with therapeutic measures (administration of the trial substances, blood transfusions, elective procedures and surgery for tumor removal).
- Overnight hospitalizations occurring exclusively for logistical reasons (e.g., no transportation available for the patient to return home on the same day).

A suspected unexpected serious adverse reaction (SUSAR) is any unexpected serious adverse reaction, that

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity

- consists of a congenital anomaly or birth defect.
- represents a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above)

11.5 Non-Serious Adverse Events of Special Interest (AESI, Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.
- Suspected transmission of an infectious agent by the study drug. Any organism, virus, or infectious particle (e.g., prion protein−transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study drug is suspected.

11.6 Pregnancy

There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. Therefore, neither pertuzumab nor trastuzumab and nab-Paclitaxel should be used during pregnancy. In patients of childbearing potential and women < 2 years after the onset of menopause, appropriate contraceptive measures are mandatory during study treatment (e.g. use single or combined non-hormonal contraceptive methods that result in a failure rate of < 1% per year or abstinence). Contraceptive measures are recommended for at least 7 months following the last dose of either trastuzumab or pertuzumab.

A female patient who becomes pregnant during the study must be instructed to stop taking the study medication and immediately inform the investigator. The investigator should report : pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of age or disease state) within 24 hours to the Sponsor. The investigator should counsel the patient, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 7 months after the completion of study medication must also be reported to the investigator.
If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.
All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the study medication should also be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

It is not known whether trastuzumab or pertuzumab is excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least 7 months following the last dose of either monoclonal antibody. No use of nab-Paclitaxel during breastfeeding.

Additional information on any pertuzumab/trastuzumab-exposed pregnancy and infant will be requested at specific time points (i.e., after having received the initial report during the first

trimester, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

11.7 Notification of Serious Adverse Events

The investigator shall report all serious adverse events (including serious adverse reactions, suspected serious adverse reactions, non-serious adverse events of special interest and pregnancies) to the sponsor immediately (**within 24 hours**) after becoming aware of them. Pregnancy shall report immediately from the investigator side. Each serious adverse event must be documented on the electronically available "Serious adverse events report" form. The completed form is automatically sent via e-mail (e-mail adress is filed in the system) to the sponsor and Alcedis GmbH. For events where electronic reporting is not possible, paper SAE forms handed out in the file at the beginning of the study are at the doctor's disposal for notification by conventional fax.

SPONSOR'S STUDY OFFICE:

Name and address study office

Universitätsklinikum Ulm
Studienzentrale
Prittwitzstr.43
D-89075 Ulm
Germany

Physicians: Dr. Amelie De Gregorio , A. Polasik, T. Romashova; Prof. Christoph Scholz, Prof. Jens Huober
Studycoordinators: Evelyn Ziel, Jessica D'Andrea, Heike Karl, Sabrina Krause

Phone: +49 (0) 731 500 58520/-58521
Fax: +49 (0) 731 500 58526
Email: studienzentrale.ufk@uniklinik-ulm.de

The initial report to the sponsor must be followed **within 5 days** by a detailed written communication (in English) containing a precise description of the side effects, all countermeasures taken and their outcome. In the event of death, if an autopsy has been performed, a copy of the autopsy report should be attached.

The sponsor will notify all **serious adverse events (SAE), non-serious adverse events of special interest (AESI) and pregnancies** immediately to the pharmaceutical manufacturer on the appropriate report forms. SAEs should be reported to Celgene within 24 hours/ (suspected) pregnancies immediately.

It is the duty of Alcedis GmbH in collaboration with the sponsor to ensure that Ethics Committee, competent authority and participating investigators are informed of all suspected unexpected serious adverse reactions (SUSARs) and all other relevant safety information in accordance with legal requirements (Section 13 GCP-V, annual reports).

12 Statistical Methods

12.1 Statistical Objectives

Primary objective (before the amendment coming into effect):
The primary objective of this study is to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy in patients with HER2-positive, hormone-receptor positive metastatic breast cancer. Safety will be assessed by the proportion of patients experiencing any adverse event (as defined by the modified adverse event score) during the treatment period.
The modified adverse event score includes all adverse events grade 3 or higher with the exception of neutropenia, which is only included if rated grade 4, and alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher.

New primary objective:
With the amendment coming into effect, the CDK4/6 inhibitor Kisquali® (ribociclib) is added to both therapy arms. Thus, the new primary objective of this study is to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisquali® (ribociclib) and standard endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy (followed by endocrine therapy plus ribociclib in combination with trastuzumab and pertuzumab as maintenance therapy) in patients with HER2-positive, hormone-receptor positive metastatic breast cancer. Tolerability will be assessed by the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period. The modified adverse event score includes all adverse events grade 3 or higher with the exception of neutropenia, which is only included if rated grade 4, and alopecia, rash, peripheral neuropathy and hand-foot syndrome, all of which are included if rated grade 2 or higher.

Main secondary objectives:
The main secondary objectives of this study are

- to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy for patients that were randomized before the amendment (i.e. the addition of ribociclib to both treatment arms) coming into effect. Tolerability will be assessed by the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period.
- to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy for all patients that were randomized (irrespectively of whether they were randomized before or after the amendment – the addition of ribociclib to both treatment arms - coming into effect). Tolerability will be assessed by the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period.

Additional secondary objectives:

- to account for the addition of Kisquali® (ribociclib), the primary analysis will be repeated (as secondary explorative analysis) using a specific modified adverse event score for the ribociclib cohort that includes nausea, vomiting, diarrhea and stomatitis grade 2 (in addition to the adverse events included in the modified adverse event score as used for the primary analysis

- to assess quality-adjusted survival (as assessed by the Q-TWiST method) and to compare it between the two treatment arms)
- to compare efficacy between the two treatment arms as assessed by overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) based on local assessment according to RECIST v1.1 in each cohort
- to assess the incidence of CNS metastases, evaluated by contrast-enhanced computer tomography (CT) or, preferably, magnetic resonance imaging (MRI) according to RECIST v1.1 based on local assessment
- to assess additional aspects of quality of life based on the evaluation of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires
- to determine presence and number of CTCs in the peripheral blood at baseline, 6 weeks after randomization, and after the 12-month study treatment period or at the time of progression, whatever comes first, and to assess the value of CTCs as indicator for therapy success
- to determine the endocrine responsiveness score (ERS) of CTCs at baseline, 6 weeks after randomization, and after the 12-month study treatment period or at the time of progression, whatever comes first, and to assess the value of the ERS as indicator for therapy success
- to evaluate and compare toxicity of both treatment arms
- to evaluate the safety and tolerability of the study treatments (all grades, all events)

All additional secondary objectives that involve comparisons between treatment arms will be performed using three different patient cohorts:
- patients that received ribociclib (i.e., patients randomized after the amendment coming into effect)
- patients that did not receive ribociclib (i.e., patients randomized before the amendment coming into effect)
- the whole study population

12.1.1 Primary Variable

Comparison of number of Adverse events with impact on the patients' quality of life as defined by the modified adverse event score between the two study arms:
- neutropenia of grade 4
- alopecia, rash, peripheral neuropathy and hand-foot syndrome, of grade 2 or higher
- all other AEs of grade 3 or higher

12.1.2 Secondary Variables

- Comparison of quality-adjusted survival between the two study arms
- Response rate: Percentage of patients showing CR, PR or SD according to RECISTv1.1 criteria in the two study arms
- ORR: Percentage of patients showing overall response (CR+PR) in the two study arms
- DCR: Percentage of patients with CR+PR + SD in the two study arms
- PFS: Time from randomization to date of first progress or death whichever occurs first
- OS: Time from randomization to date of death
- Assessment of Quality of life over time as defined by EORTC QLQ-C30 and EORTC QLQ-BR23
- CTC prevalence at different time points
- ERS: endocrine responsiveness score of CTCs at different time points

12.2 Study Populations

The following study population sets will be examined:

Intention to Treat (ITT) Set: All randomized patients will be included in the ITT population.

Safety Set: All randomized patients who received at least one dose of the study treatment and have at least one post-baseline safety assessment (the statement that a patient had no adverse events on the Adverse Event CRF is also regarded as a safety assessment). Patients who do not receive any amount of study medication will be excluded from the safety population.

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

If necessary, modified or additional analysis sets may be specified in a Statistical Analysis Plan (SAP) prior to data base lock.

12.3 Statistical Methods

Statistical analysis of experimental data will be performed at the end of the studies. For all parameters, descriptive statistics will be provided (absolute and relative frequencies for categorial data; number of valid and missing observations, means, standard deviations, medians, interquartiles, ranges, and confidence intervals – as appropriate – for continuous variables). Time-to-event data will be analysed using the Kaplan-Meier method and summarized using medians, 95% confidence limits, and Kaplan-Meier survival plots.
The (new) primary objective of this study is to assess the tolerability of a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus Kisquali® (ribociclib) and standard endocrine therapy as compared to a dual HER2-targeted therapy with Herceptin® (trastuzumab) and Perjeta® (pertuzumab) plus chemotherapy (followed by endocrine therapy plus ribociclib in combination with trastuzumab and pertuzumab as maintenance therapy) in patients with HER2-positive, hormone-receptor positive metastatic breast cancer. In the primary confirmatory analysis, the proportion of patients experiencing any adverse event as defined by the modified adverse event score during the treatment period (i.e. the relative risk) will be compared between the two treatment arms using the χ^2 test, and both relative risk ratio and the corresponding 95% confidence interval will be reported. In addition, pre-specified explorative subgroup analyses will be conducted to compare the proportion of patients experiencing any adverse event (as defined by the modified adverse event score) during the treatment period between the two treatment arms in the prospectively defined subgroups (according to the stratification factors) of patients with and without visceral metastases, of patients in the first line and in higher lines of chemotherapy treatment, and of patients with and without previous therapy with trastuzumab.
The primary confirmatory analysis will be performed for all patients randomized after the amendment (i.e., the addition of ribociclib in both treatment arms) comes into effect (see statistical objectives).

According to the two main secondary study objectives stated above (see statistical objectives), this analysis will also be performed for the subset of patients randomized before the amendment coming into effect (i.e., all patients that did not receive ribociclib as part of the study treatment) and with the full safety and/or ITT set of patients (i.e., all patients randomized for this study).

All analyses regarding the additional secondary objectives will have exploratory character only and will be performed using the following three different patient cohorts:

- patients that received ribociclib (i.e., patients randomized after the amendment coming into effect)

- patients that did not receive ribociclib (i.e., patients randomized before the amendment coming into effect)
- all randomized patients

The statistical methods described in the following section are appropriate for the data and distributions usually expected in this type of trials.
All secondary endpoints and other outcomes that are calculated based on frequencies/rates (ORR, DCR, CR, PR, SD) will be summarized using frequency tables presenting absolute and relative frequencies together with appropriate confidence intervals. Comparisons between groups will be performed using suitable non-parametric statistical tests such as Fisher's exact test, χ^2-test, or Cochran-Mantel-Haenszel test.
The key secondary endpoint - quality-adjusted survival (QAS) - will be analyzed using the quality-adjusted time without symptoms and toxicity (Q-TWiST) analysis method (see Goldhirsch et al. 1989; Glasziou et al. 1990; Gelber et al. 1993). Overall survival is partitioned into distinct clinical health states that differ in quality of life. Mean duration of each health state is then estimated using the Kaplan-Meier method, and the duration of each state is then weighted based on utility coefficients that represent the perceived quality of life value of each health state to the patients. QAS is then calculated by summing up the weighted health state durations, and thus represents a single metric value that is a composite measure of both quantity (i.e. duration) and quality of life. There are several methods of obtaining the utility coefficients for the different health states. The method with the highest validity is to prospectively assess utility coefficients based on direct evaluations from the subjects that participate in the clinical trial (Revicki et al. 2006). This method will be applied here by calculating utility coefficients based on the results of the EORTC QOL-C30 questionnaire that the patients have to fill in at multiple time points during the study. In addition, a threshold utility analysis will be performed that illustrates the potential outcome of the QAS comparison between the two treatment arms given various combinations of utility coefficients.
Besides the Q-TWiST analysis, additional quality of life (QoL) analyses will be performed based on the EORTC QLQ-C30 and BR23 questionnaires. The raw scores will be transformed to scores ranging from 0 to 100 following the instructions of the respective manuals. Descriptive statistics will be used to summarize both the single-item measures and multi-item scales at each scheduled assessment time point. Additionally, changes in QoL data between baseline scores and the scores obtained at the scheduled time points after start of the study treatment will be summarized for all patients with an evaluable baseline score and at least one evaluable post-baseline score. Longitudinal changes in QoL will be assessed using appropriate generalized linear mixed models with individual patients being fitted as random factors.
The presence and number of circulating tumor cells (CTCs) measured at different time points will be evaluated in a descriptive way. The temporal changes in the number of CTCs will be described and analysed using appropriate generalized linear mixed models. In addition, different measures of CTC dynamics (based on various threshold values, relative or absolute changes in CTC counts) and their value for evaluating therapy efficacy or as a prognostic tool will be examined in detail by explorative data analyses.
Progression-free and overall survival will be estimated by the Kaplan Meier product limit method, and median values, 95% confidence intervals and survival plots will be provided. When appropriate, progression-free and overall survival will be compared between groups using the logrank test, and additional multivariate analyses may be performed by suitable regression models (proportional hazard regression model, logistic regression).
More details will be provided in a Statistical Analysis Plan (SAP) which will be finalized prior to data base lock.
Unless otherwise noted, all statistical calculations will be implemented using the SPSS system (IBM Cooperation, New York, USA).

12.4 Sample Size

The study is designed as a two-arm parallel phase III randomized superiority trial. The main primary objective is to analyse (using the χ^2-test) whether the proportion of patients that are affected by adverse events as defined by the modified adverse event score (assessed based on NCI CTCAE Version 4.03) differs between the dual HER2-targeted plus endocrine-based treatment arm and the dual HER2-targeted plus chemotherapy treatment arm. The sample size calculations are based on the assumption that the probability of having an adverse event as defined by the modified adverse event score for patients with HER2 positive metastatic breast cancer treated with dual HER2-targeted plus chemotherapy is 86.3% (based on results of the CLEOPATRA trial; data provided by Roche). Based on this assumption, a minimum of 121 patients per treatment arm is required to detect a 20% decreased risk of having an adverse event as defined by the modified adverse event score (i.e. a relative risk ratio of 0.8) for patients treated with dual HER2-targeted plus endocrine therapy as compared to patients treated with dual HER2-targeted plus chemotherapy (90% power, two-sided test, $\alpha = 0.05$).
According to national and international guidelines, the use of endocrine therapies is preferred in the non-curable metastatic setting whenever possible due to the lower toxicity as compared to cytotoxic treatment options (e.g. NCCN Guidelines Breast Cancer Version 3.2013; International consensus guidelines for advanced breast cancer, Cardoso et al. 2012). As there is currently no consensus on how to calculate a minimum clinically important difference (MCID) to be used for sample size calculations in clinical trials, the clinical relevance of a difference to be detected in a clinical trial has to be judged based on clinical expertise. The current clinical judgement in standard of care strongly suggests that a difference of 20% in the risk of experiencing an adverse event is highly relevant for therapeutic decisions.
Assuming a loss to follow-up rate of about 10%, 270 patients with HER2 positive and hormone-receptor positive metastatic breast cancer have to be recruited for this study. Sample size calculations were performed with PASS 12 (NCSS Statistical Software LLC, Kaysville, Utah, USA).

Due to the amendment with the addition of ribociclib to both randomization arms, a separate sample size calculation was performed to assess the statistical power for the new primary analysis for the ribociclib cohort. It is assumed that 90 patients will be recruited before the amendment comes into effect (i.e. these patients do not receive ribociclib). Accordingly, 180 patients will receive ribociclib. Based on the assumption that the probability of having an adverse event as defined by the modified adverse event score for patients with HER2 positive metastatic breast cancer treated with dual HER2-targeted plus chemotherapy is 86.3% (see above), a sample size of 80 patients per treatment arm (180 patients receiving ribociclib, about 10% loss to follow-up assumed) will result in 76% power (two-sided test, $\alpha = 0.05$) to detect a 20% decreased risk of having an adverse event as defined by the modified adverse event score (i.e. a relative risk ratio of 0.8) for patients treated with dual HER2-targeted plus ribociclib and standard endocrine therapy as compared to patients treated with dual HER2-targeted plus chemotherapy followed by endocrine therapy plus ribociclib in combination with trastuzumab and pertuzumab as maintenance therapy.

12.5 Interim Analysis

After the amendment (addition of ribociclib in both randomization arms) comes into effect, an interim analysis will be performed after inclusion of 15 patients in the chemotherapy cohort.

13 Sub-Studies

There are no sub-studies planned.

14 Data Management

14.1 Patient Identification

All data related to patients will be assessed pseudonymously. Each patient will be clearly identified through the patient number given in the enrolment procedure. At the centre site the investigator compiles a confidential list, in which the patient name and address is assigned to the patient number.

14.2 Data Collection

The data management for this study will be performed by Alcedis GmbH, Winchesterstr. 3, D-35394 Gießen.
The following chapters describe the software employed and measures applied for data security.
Data are recorded, processed and stored using the following software tools.
a. CRF database (Location: Alcedis)
b. SAE database (Location: Alcedis)
Wherever applicable, current GCP guidelines, actual technical standards and guidelines are observed.

14.3 Employed Software

CRF database

For data capturing and data management of this clinical trial, a web-based validated software (WBDC) 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 CRFs 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 SAE data.

c) **Reports:** Dynamic report generator, e.g. reports for investigators on CRF status.

d) **Database:** Relational database for data management. The data from the relational database will be retrieved using the export engine of *Alcedis Med* and thereafter converted into data sets for further validation and analysis.

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.

14.4 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 CRF 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 CRF 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 backup 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.

15 Monitoring

15.1 Monitoring

Study monitoring is undertaken by monitors appointed by ALCEDIS GMBH. The responsible monitor will be allowed, on request, to inspect the various records of the trial (Case Report Forms 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.

15.2 Audit, Inspections

The sponsor retains the right to undertake a quality audit in accordance with ICH-GCP guidelines at any time, particularly if any doubt should arise about the quality of the documentation.

In such an audit, as with an audit by the competent supervisory or health authorities, the authorized representatives involved should be granted access to the originals of the patient files. The investigator guarantees his full co-operation in the event of an audit.

16 Ethical Considerations

16.1 Declaration of Helsinki

The study is conducted in accordance with the 1996 Declaration of Helsinki (Somerset West, Republic of South Africa).

16.2 Patient Information

An unconditional prerequisite for a patient participating in the study is her written informed consent. Adequate information must therefore be given to the subject by the investigator before informed consent is obtained. A person designated by the investigator may give the information, if permitted by local regulations. A patient information sheet in the local language will be provided for the purpose of obtaining informed consent. In addition to this written information, the investigator or his designate will inform the patient verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons.
The patient information sheet will be revised whenever important new information becomes available that may be relevant to the consent of patients.

The written informed consent of the patient to participate in the clinical study has to be given before any study-related activities are carried out. It must be signed and personally dated by the patient and by the investigator/person designated by the investigator to conduct the informed consent discussion. Patients are also asked to give consent to additional analysis of tumour material. This approval is not a precondition for participation in the study.

Provision of consent will be confirmed in the eCRF by the investigator. The signed and dated declaration of informed consent will remain at the investigator's site and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the subject prior to participation.

16.3 Consent to Participate

Each patient must give their written consent to participate in the study. At the same time, the patient must be given sufficient time and opportunity to decide on their participation and to clarify any outstanding questions before the institution of any study procedures.

The declaration of consent is signed by the patient and the study doctor.

The patient informed consent is presented in duplicate. One copy remains with the investigator and the other must be given to the patient.

16.4 Use, Storage and Transmission of Data

Patients will be informed that data, related to their illness, will be saved and in anonymous form used for scientific analysis and publications.
Patients are entitled to get information about the saved data.

The informed consent to data security and data transfer will be given apart of the informed consent to study participation.

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.

17 Legal and Administrative Regulations

17.1 Coordinating Investigator according to Local Law

Prof. Dr. Jens Huober
University Hospital Ulm
Department of Gynecology and Obstetrics
Prittwitzstr.43
D-89075 Ulm

The coordinating investigator can demonstrate at least 2 years' experience in the clinical testing of medicinal products.

17.2 Compliance with the Protocol and Good Clinical Practice Guidelines

The treatment should be conducted exactly as in the protocol. Exceptions to this are emergency situations in which the concern for the safety and well-being of the patients makes alternative treatment necessary. Any protocol deviation must be reported.

The recommendations of Good Clinical Practice (see ICH-GCP: International Conference on Harmonisation - Good Clinical Practice), valid since 17.1.1997, must be observed.

17.3 Protocol Supplements

Supplements or changes to the protocol may only be made by the coordinating investigator and submitted to the Ethics Committees and the national competent authorities as an amendment to the protocol.

17.4 Study Monitoring

The sponsor and the investigators must ensure the clinical trial is conducted correctly. The state of progress of the study must be presented at study meetings.

17.5 Specialist Qualification of Investigators and Suitability of Study-Centres

All participating investigators must demonstrate the suitability of the study centre in accordance with the local law and the GCP Ordinance.

17.6 Maintenance of a Study File

The investigator will keep all study-relevant documents (e.g. study plan, curriculum vitae, ethics committee approval) and correspondence in a special study file.

17.7 Authorisation by the Competent Authorities

The documents on the pharmacological and toxicological testing of study medication are filed with the Competent Authorities in accordance with local law. The application for approval of a clinical trial with a medicinal product for human use is made on behalf of the sponsor by Alcedis GmbH.

17.8 Ethics Committee Approval

Before the beginning of the study, an application for approval will be submitted to the Ethics Committees of the coordinating investigator and to the ethics committees of the participating investigators.

17.9 Notification to the Local Authorities

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.

17.10 Archival

The investigator is legally obliged to keep the patient identification list for at least 10 years after the end of the study. The patient data recorded, including the original or copies of test results, the informed consents, the ethics committee approval and the correspondence and other original documents associated with the study must also be stored by the investigator for a period of 10 years. This precondition also applies if the doctor transfers the documents (and the associated obligation of storage) to a successor.

Original data from the study patients (patient records) must be stored in accordance with the archiving period applicable in the study centres, but for not less than 10 years.

17.11 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.

17.12 Confidentiality

The contents of the study protocol and case report form must be treated confidentially and may not be disclosed to unauthorised parties either verbally or in writing.

17.13 Patient Insurance

The study patients are insured at the *"HDI Gerling Industrie Versicherung AG"* in accordance with the local law up to a sum of € 500,000.00.

HDI-Gerling Industrie Versicherung AG
Riethorst 2; 30659 Hannover
Tel. 0511-645-0
Fax 0511-645-4545
Web: www.hdi-gerling.de
Policy Number: 57 010315 03015 (Anmeldenummer 1302 2014 110)

17.14 Honorarium for Clinical Trial Participants

Patients are not remunerated for study participation.

17.15 Final Report/Publications

Once the final biometric report is available, the final medical report will be compiled by the study director.

The results of the study will be published in general publications. The order in which the authors are listed will be based on the number of patients they have included. A co-author will be included in the list of authors for each centre in which more than 5 patients are included.

17.16 Third Party Financing

This is an investigator initiated trial. The study will be sponsored by the University of Ulm, Germany.

Roche provides the study medication Perjeta® (pertuzumab) free of charge, except for the authorized use (Herceptin® + Perjeta® + docetaxel in the first line treatment). Roche also provides financial support.

Novartis provides the study medication ribociclib free of charge. Novartis also provides financial support.

This project is conducted with support from the Investigator-Initiated Study Program of Janssen Diagnostics LLC, Raritan NJ, USA.

Celgene provides Abraxane® free of charge for a combination therapy with Herceptin® and Perjeta®. Celgene also provides financial support.

Eisai provides Halaven® free of charge for a combination therapy with Herceptin® and Perjeta®, Eisai also provides financial support.

This study entails no additional financial expenditure for supplementary laboratory analyses or additional diagnostic measures associated with the therapy, as the study design is deliberately based on the procedure for the cytostatic therapy administered in the previous standard.

18 Literature

Aaronson NK Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology [Artikel] // J Natl Cancer Inst. - 1993. - 85(5):365-76.

Agus DB Gordon MS, Taylor C et al. Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer [Artikel] // J Clin Onco. - 2005. - 23(11):2534-43.

Arpino G, Ferrero J-M, la Haba-Rodriguez, Easton V, Schumacher C et al. A randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first-line patients with HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer //SABCS 2016

Austreid E1 Lonning PE, Eikesdal HP The emergence of targeted drugs in breast cancer to prevent resistance to endocrine treatment and chemotherapy [Artikel] // Expert Opin Pharmacother. - 2014. - 15(5):681-700.

Baselga J Cortés J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer [Artikel] // N Engl J Med. - 2012. - 366:109–119.

Bidard FC Mathiot C, Delaloge S et al. Single circulating tumor cell detection and overall survival in nonmetastatic breast cancer [Artikel] // Ann Oncol. - 2010. - 21(4):729-33.

Botteri E Sandri MT, Bagnardi V et al. Modeling the relationship between circulating tumour cells number and prognosis of metastatic breast cancer [Artikel] // Breast Cancer Res Treat. - 2010. - 122(1):211-7.

Bottomley A Biganzoli L, Cufer T et al. European Organization for Research and Treatment of Cancer Breast Cancer Group. Randomized, controlled trial investigating short-term health-related quality of life with doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chem [Artikel] // J Clin Oncol. - 2004. - 22(13):2576-86.

Burstein HJ Winer EP The distinctive nature of HER2 positive breast cancer [Artikel] // NEJM. - 2005. - 353 (16): 1652-54.

Bartkova J, LukasJ, Müller H et al. Cyclin D1 protein expression and function in human breast cancer. //Int J Cancer. 1994 May 1;57(3):353-61.

Buckley MF, Sweeney KJ, Hamilton JA, Sini RL,et al. Expression and amplification of cyclin genes in human breast cancer.// Oncogene. 1993 Aug;8(8):2127-33.

Cobleigh M Vogel C, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2 overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease [Artikel] // J Clin Oncol. - 1999. - 17: 2639-2648.

Conroy T Mercier M, Bonneterre J et al. French version of FACT-G: validation and comparison with other cancer-specific instruments [Artikel] // Eur J Cancer. - 2004. - 40(15):2243-52.

Cristofanilli M Budd GT, Ellis MJ et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer [Artikel] // N Engl J Med. - 2004. - 351(8):781-91.

Eisenhauer EA Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). [Artikel] // Eur J Cancer. - 2009. - 45(2):228-47.

Fehm T Müller V, Aktas B et al. HER2 status of circulating tumor cells in patients with metastatic breast cancer: a prospective, multicenter trial [Artikel] // Breast Cancer Res Treat. - 2010. - 124(2):403-12.

Finn et al., Abstract 507, oral presentation at ASCO 2016, Chicago.

Garg A, Li J et al. Exposure-response analysis of pertuzumab in HER2-positive metastatic breast cancer:absence of effect on QTc prolongation and other ECG parameters.//Cancer Chemother Pharmacol (2013) 72:1133-1141.

Gelber RD Goldhirsch A, Cole BF. Evaluation of effectiveness: Q-TWiST. The International Breast Cancer Study Group [Artikel] // Cancer Treat Rev . - 1993. - 19 Suppl A:73-84.

Gianni L, Bisagni L et al. Neo-adjuvant treatment with trastuzumab and pertuzumab associated with palbociclib and fulvestrant in HER2-positive and ER-positive breast cancer: Effect on Ki67 during and after treatment. A phase II Michelangelo study //2016 Abstract, SABCS.

Gillet C, Fantl V, Smith R, et al. Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining.// Cancer Res. 1994 Apr 1;54(7):1812-7.

Gillet C, Smith P, Gregory W, Richards M, et al. Cyclin D1 and prognosis in human breast cancer.// Int J Cancer. 1996 Apr 22;69(2):92-9.

Giuliano M Giordano A, Jackson S et al. Circulating tumor cells as prognostic and predictive markers in metastatic breast cancer patients receiving first-line systemic treatment [Artikel] // Breast Cancer Res. - 2011. - 13(3):R67.

Glasziou PP Simes RJ, Gelber RD Quality adjusted survival analysis [Artikel] // Stat Med. - 1991. - 9(11):1259-76.

Goldhirsch A Gelber RD, Simes RJ et al. Costs and benefits of adjuvant therapy in breast cancer: a quality-adjusted survival analysis [Artikel] // J Clin Oncol. - 1989. - 7(1):36-44.

Goldhirsch A Winer EP, Coates AS et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 [Artikel] // Ann Onc. - 2013. - 24: 2206-2223.

Gradishar WJ, Tjuladin S, Davidson N et al. Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel compared with polyethylated Castor Oil-Based Paclitaxel in women with breast cancer. [Artikel] //J of Clincal Onc.-200523:7794-7803.

Graus-Porta D Beerli RR, Daly JM, Hynes N ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling [Artikel] // EMBO J. - 1997. - 16:1647-1655.

Hayes DF Cristofanilli M, Budd GT et al. Circulating tumor cells at each follow-up time point during therapy of metastatic breast cancer patients predict progression-free and overall survival [Artikel] // Clin Cancer Res. - 2006. - 15;12(14 Pt 1):4218-24.

Hjermstad MJ Fossa SD, Bjordal K et al. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire [Artikel] // J Clin Oncol. - 1995. - 13(5):1249-54.

Hortobagyi GN Treatment of breast cancer [Artikel] // NEJM. - 1998. - 339 (14): 974-84.

http://globocan.iarc.fr/ Pages/fact_sheets_cancer.aspx; assessed 07.03. [Buch]. - 2014.

Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-line Therapy for HR-positive, advanced breast cancer. //N Engl J Med 2016 Nov 3; 375 (18): 1738-1748.

Huober J Fasching PA, Barsoum M et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer - results of the eLEcTRA trial [Artikel] // Breast. - 2012. - 21(1):27-33.

Huschka MM Mandrekar SJ, Schaefer PL et al. A pooled analysis of quality of life measures and adverse events data in north central cancer treatment group lung cancer clinical trials [Artikel] // Cancer. - 2007. - 109(4):787-95.

Hynes NE Stern DF The biology of erbB-2/neu/HER-2 and its role in cancer [Artikel] // Biochim Biophys Acta. - 1994. - 1198:165-184.

Junttila TT Akita RW, Parsons K et al. Ligand-independent HER2/HER3/PI3K complex is disrupted by trastuzumab and is effectively inhibited by the PI3K inhibitor GDC-0941 [Artikel] // Cancer Cell 2009; 15(5. - 2009. - 15(5):429-40.

Kaufman B Mackey JR, Clemens MR et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study [Artikel] // J Clin Oncol 2009. - 2009. - 27(33):5529-37.

Kazuhiro Araki, Ippei Fukada et al. First report of eribulin in combination with pertuzumab and trastuzumab for advanced HER2-positive breast cancer//Breast 2017 Oct; 35: 78-84

Lemieux J Beaton DE, Hogg-Johnson S et al. Responsiveness to change [corrected] due to supportive-expressive group therapy, improvement in mood and disease progression in women with metastatic breast cancer [Artikel] // Qual Life Res. - 2007. - 16(6):1007-17.
Liu MC Shields PG, Warren RD et al. Circulating tumor cells: a useful predictor of treatment efficacy in metastatic breast cancer [Artikel] // J Clin Oncol. - 2009. - 27(31):5153-9.
Lundgren K, Brown M, Pineda S, et al. TransATAC investigators. Effects of cyclin D1 gene amplification and protein expression on time to recurrence in postmenopausal breast cancer patients treated with anastrozole or tamoxifen: a TransATAC study. Breast Cancer Res. 2012 Apr 4;14(2):R57.
Marty M Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group [Artikel] // J Clin Oncol.. - 2005. - 23: 4265–4274.
McLachlan SA Devins GM, Goodwin PJ Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) as a measure of psychosocial function in breast cancer patients [Artikel] // Eur J Cancer. - 1998. - 34(4):510-7.
Meric F Hung MC, Hortobagyi GN, Hunt KK. HER2/neu in the management of invasive breast cancer [Artikel] // J Am Coll Surg.. - 2002. - 194(4):488-501.
Miller TW, Balko JM, Fox EM, et al. ERα-dependent E2F transcription can mediate resistance to estrogen deprivation in human breast cancer.// Cancer Discov. 2011 Sep;1(4):338-51. doi: 10.1158/2159-8290.CD-11-0101. Epub 2011 Jul 20.
Musgrove EA, Caldon CE, Barraclough J, et al . Cyclin D as a therapeutic target in cancer. // Nat Rev Cancer 2011 11:558-72.
Nahta R Hung MC, Esteva FJ The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells [Artikel] // Cancer Res. - 2004. - 64(7):2343-6.
Osoba D Rodrigues G, Myles J et al. Interpreting the significance of changes in health-related quality-of-life scores [Artikel] // J Clin Oncol 1998. - 1998. - 16(1):139-44.
Pierga JY1 Hajage D, Bachelot T et al. High independent prognostic and predictive value of circulating tumor cells compared with serum tumor markers in a large prospective trial in first-line chemotherapy for metastatic breast cancer patients [Artikel] // Ann Oncol. - 2012. - 23(3):618-24.
Roche Investigator's Brochure Perjeta®, 12th Version, February [Buch]. - 2013.
Roche Investigator's Brochure Herceptin, Fourteenth Version, October [Buch]. - 2013.
Scheuer W Friess T, Burtscher H et al. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models [Artikel] // Cancer Res . - 2009. - 69(24):9330-6.
Slamon D Leyland-Jones B, Shak S, et al Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2 [Artikel] // N Engl J Med. - 2001. - 344: 783-792.
Slamon DJ Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. [Artikel] // NEJM. - 2001. - 344(11):783-92.
Spector NL Blackwell KL Understanding the mechanisms behind trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer [Artikel] // J Clin Oncol. - 2009. - 27:5838–5847.
Swain SM Kim SB, Cortés J et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study [Artikel] // Lancet Oncol 2013. - 2013. - 14: 461–71.
Swain SM, Ewer MS, Cortés J et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study [Artikel] // Oncologist. – 2013b. - 18:257-64.

Turner NC, et al., Palbociclib in hormone-receptor-positive advanced breast cancer.// N Engl J Med 2015 373(3): 209-219
Yu Q, Sicinska E, Geng Y et al. Requirement for CDK4 kinase function in breast cancer. //*Cancer Cell*. 2006 Jan;**9**(1):23-32.

19 Appendices

19.1 NCI-CTC-Toxicity Criteria Version 4.0

It is recommended to follow the “Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0” that can be found online at the following address:

http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

19.2 ECOG/Karnofsky-Index

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.

19.3 Quality of life Assessment (EORTC QLQ-C 30 + BR23)

Introduction

Possible prolongation of survival due to additional treatment with Trastzumab/Pertuzumab must be appraised in the light of contingent side effects, which may lower patients' quality of life. To evaluate eventual efficacy of everolimus, 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: | | | | |

Dokumentationsbögen für die Lebensqualität

Eine multizentrische, randomisierte Phase III-Studie zum Vergleich einer Chemo- versus einer endokrinen Therapie in Kombination mit einer dualen HER2-gerichteten Herceptin® (Trastuzumab)/ Perjeta® (Pertuzumab)-Therapie bei Patientinnen mit HER2-positiven und hormonrezeptorpositiven metastasiertem Brustkrebs.

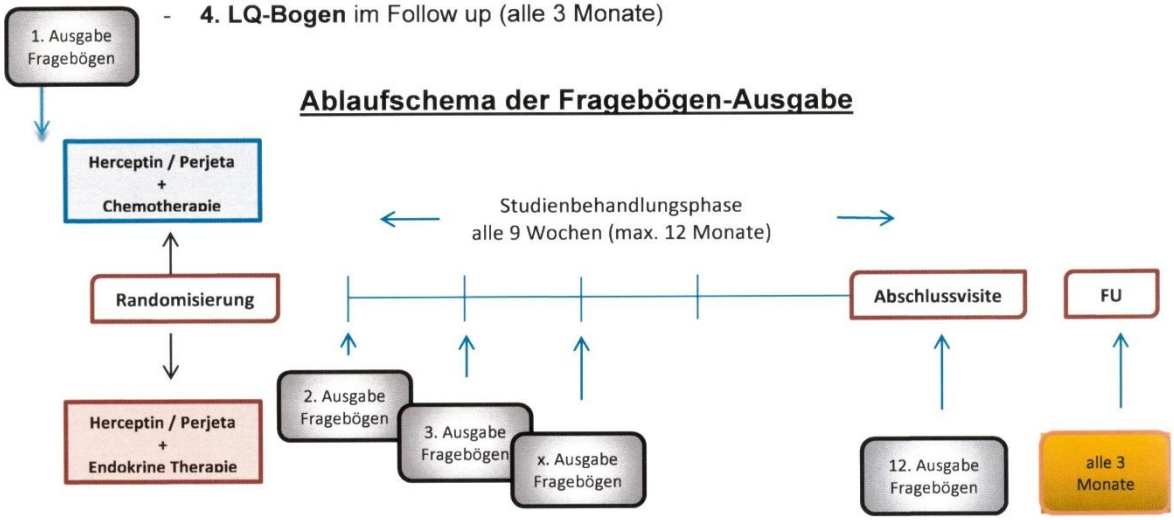
DETECT V / CHEVENDO

An die/ den behandelnde(n) Ärztin/ Arzt:

- Bitte tragen Sie das Geburtsjahr, Zentrums- und Patientennummer sowie das Datum in die LQ-Bögen, die Sie den Patientinnen geben, ein.

- Bitte die ausgefüllten LQ-Bögen mittels beigelegter Umschläge an die **Alcedis GmbH** senden.
  - **1. LQ-Bogen** zum Screening (vor der Randomsierung)
  - **2. LQ-Bogen** vor Kontrollvisiten (alle 9 Wochen)
  - **3. LQ-Bogen** Abschlussvisite (12 Monate nach 1.Dosis oder bei vorzeitigem Therapieabbruch (z.B. bei Progress)
  - **4. LQ-Bogen** im Follow up (alle 3 Monate)

Ablaufschema der Fragebögen-Ausgabe



! Bitte senden Sie die LQ-Bögen alle 3 Monate an die Alcedis GmbH.
Der Durchschlag ist zum Verbleib im Zentrum bestimmt.

Vielen Dank für Ihre Mitarbeit!

DETECT V/CHEVENDO

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

Erhebung der Lebensqualität:

Vor Randomisierung ☐ **vor**_____. Zyklus / Kontrollvisite ☐

Abschlussvisite ☐ **Follow up Monat** _____. ☐

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

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 V/CHEVENDO

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 gemeinsamen 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 V/CHEVENDO

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

Erhebung der Lebensqualität:

Vor Randomisierung ☐ **vor**_____. Zyklus / Kontrollvisite ☐

Abschlussvisite ☐

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

EORTC QLQ-BR23

Patientinnen berichten manchmal die nachfolgend beschriebenen Symptome oder Probleme. Bitte beschreiben Sie, wie stark Sie diese Symptome oder Probleme während 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 nackt 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 V/CHEVENDO

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, trockene oder schuppende Haut)?	1	2	3	4

DETECT V/CHEVENDO

19.4 Deutsche Protokoll-Synopse

EudraCT-Nr.: 2014-002249-22	**Protokoll-Nr.:** D-V
Studientitel	Eine multizentrische, randomisierte Phase III-Studie zum Vergleich einer Chemo- versus einer endokrinen Behandlung in Kombination mit einer dualen HER2-gerichteten Herceptin® (Trastuzumab)/ Perjeta® (Pertuzumab)-Therapie plus Kisqali® (Ribociclib) bei Patientinnen mit HER2-positivem und hormonrezeptorpositivem metastasiertem Brustkrebs.
Sponsor	Universitätsklinikum Ulm**,** Prof. Dr. Wolfgang Janni
Leiter der klinischen Prüfung	Prof. Dr. Jens Huober**,** Universitätsklinikum Ulm
Studiendesign	Prospektive, offene, multizentrische, randomisierte klinische Phase IIIa-Studie
FDA “covered study”	☐ ja ☒ nein
Prüfzentren	Bis zu 120 Prüfzentren deutschlandweit
Geplante Studiendauer	Start Studieneinschluss: Q3 / 2015 Ende Studieneinschluss: Q2 / 2020 Studienbehandlungssdauer: 12 Monate Ende Behandlungsperiode: Q2/ 2021 Follow-up Dauer: 24 Monate Ende Follow-up Periode: Q2 / 2023
Rationale der Studie	**Primärer Studienendpunkt (vor Inkrafttreten des Amendments):** Das primäre Zielkriterium dieser Studie ist, die Verträglichkeit der dualen HER2-gerichteten Therapie (Trastuzumab plus Pertuzumab) in Kombination mit einer endokrinen Therapie versus der dualen HER2-gerichteten Therapie in Kombination mit einer Chemotherapie bei Patientinnen mit HER2-positivem, hormon-rezeptor positivem metastasiertem Brustkrebs zu evaluieren. „Sicherheit/Verträglichkeit wird über den Anteil an Patientinnen mit unerwünschten Ereignissen (adverse events) während des Behandlungszeitraums definiert (Definition nach dem modifizierten „adverse event score“).“ Der modifizierte „adverse event score“ beinhaltet alle unerwünschten Ereignisse mit Grad 3 oder höher, mit der Ausnahme von Neutropenie, welche nur bei Grad 4 gewertet wird, und Haarausfall, Hautausschlag, periphere Neuropathie sowie Hand-Fuß-Syndrom, welche schon ab Grad 2 gewertet werden. **Neuer primärer Studienendpunkt:** Mit Inkrafttreten des Amendments bekommen neu eingeschlossene Patientinnen in beiden

	Randomisierungsarmen zusätzlich den CDK4/6 Inhibitor Kisquali® (Ribociclib). Daher wird als neues primäres Studienziel die Verträglichkeit der dualen HER2-gerichteten Therapie (Trastuzumab plus Pertuzumab) in Kombination mit Ribociclib und endokriner Therapie versus der dualen HER2-gerichteten Therapie in Kombination mit einer Chemotherapie (gefolgt von einer Erhaltungstherapie mit Trastuzumab und Pertuzumab plus Ribociclib und endokrine Therapie) verglichen. Sicherheit/Verträglichkeit wird über die Anzahl an unerwünschten Ereignissen (adverse events) während des Behandlungs-zeitraums definiert (Definition nach dem modifizierten „adverse event score“; siehe oben). **Sekundäre Hauptendpunkte:** • Vergleich der Verträglichkeit der dualen HER2-gerichteten Therapie (Trastuzumab plus Pertuzumab) in Kombination mit einer endokrinen Therapie versus der dualen HER2-gerichteten Therapie in Kombination mit einer Chemotherapie bei Patientinnen, die vor Inkrafttreten des Amendments in die Studie eingeschlossen wurden (diese Patientinnen haben kein Ribociclib im Rahmen ihrer Studienbehandlung erhalten). Sicherheit/Verträglichkeit wird über die Anzahl an unerwünschten Ereignissen (adverse events) während des Behandlungszeitraums definiert (Definition nach dem modifizierten „adverse event score“; siehe oben). • Vergleich der Verträglichkeit der dualen HER2-gerichteten Therapie (Trastuzumab plus Pertuzumab) in Kombination mit einer endokrinen Therapie versus der dualen HER2-gerichteten Therapie in Kombination mit einer Chemotherapie bei allen in die Studie eingeschlossenen Patientinnen (unabhängig davon, ob sie vor oder nach Inkrafttreten des Amendments eingeschlossenwurden). Sicherheit/Verträglichkeit wird über die Anzahl an unerwünschten Ereignissen (adverse events) während des Behandlungszeitraums definiert (Definition nach dem modifizierten „adverse event score“; siehe oben). **Weitere sekundäre Endpunkte:** • Vergleich der Verträglichkeit der dualen HER2-gerichteten Therapie (Trastuzumab plus Pertuzumab) in Kombination mit Ribociclib und endokriner Therapie versus der dualen HER2-gerichteten Therapie in Kombination mit einer Chemotherapie (gefolgt von einer Erhaltungstherapie mit Trastuzumab und Pertuzumab plus Ribociclib und endokrine Therapie), wobei Sicherheit/Verträglichkeit anhand eines speziellen „adverse event score“

	evaluiert wird, der zusätzlich zu den im modifizierten „adverse event score“ beinhalteten unerwünschten Ereignissen (siehe oben) auch Übelkeit, Erbrechen, Durchfall und Stomatitis ab Grad 2 beinhaltet. • Bestimmung des quality-adjusted survival (Auswertung nach der Q-TWiST Methode) und der Unterschied des quality-adjusted survival im Vergleich zwischen den Behandlungsarmen • Unterschiede zwischen den Behandlungsarmen hinsichtlich der Allgemeinen Ansprechrate (ORR), der klinischen Erfolgsrate (DCR), des Progressionsfreien Überlebens (PFS) und des Gesamtüberlebens (OS) entsprechend den RECIST Leitlinien Version 1.1., basierend auf lokaler Beurteilung. • Beurteilung der Inzidenz von ZNS-Metastasen, mittels CT oder vorzugsweise MRT entsprechend den RECIST Leitlinien Version 1.1., basierend auf lokaler Beurteilung. • Weitere Beurteilung zusätzlicher Lebensqualitätsaspekte auf Basis der EORTC QLQ-C30 und EORTC QLQ-BR23 Fragebögen • Vorkommen und Anzahl der CTCs im peripheren Blut vor Behandlungsbeginn, 6 Wochen nach Randomisierung, und nach der 12-monatigen Studienbehandlungsdauer oder bei Progress (falls dieser vor Ende der 12-monatigen Studienbehandlungsdauer eintritt) zur Evaluierung der Aussagekraft der CTCs hinsichtlich des Therapieansprechens/- erfolgs. • Bestimmung des endocrine responsiveness score (ERS) der CTCs vor Behandlungsbeginn, 6 Wochen nach Randomisierung, und nach der 12-monatigen Studienbehandlungsdauer oder bei Progress (falls dieser vor Ende der 12-monatigen Studienbehandlungsdauer eintritt) zur Evaluierung der Aussagekraft der ERS hinsichtlich des Therapieansprechens/- erfolgs • Toxizitätsanalyse und Vergleich der Toxizität beider Behandlungsarme • Evaluation der Sicherheit und Verträglichkeit der Studienmedikation
Geplante Patientenzahl	Insgesamt 270 Patientinnen
Patientenauswahl Behandlungschema und Dosierung	**Einschlusskriterien:** Patientinnen können nur eingeschlossen werden, wenn **alle** der folgenden Kriterien erfüllt werden: • Schriftliches Einverständnis zur Studienteilnahme • Bestimmung des HER2-Status des primären Mammakarzinoms und/oder einer Metastase mit **HER2-Positivität** der Gewebsproben, d.h. Immunhistochmie 3+ oder Fluoreszenz in situ Hybridisierung (FISH) positiv sowie

	histopathologisch bestätigter **Hormonrezeptorpositivität** • Metastasiertes Mammakarzinom, das einer Operation oder Strahlentherapie alleine nicht zugänglich ist • Nicht mehr als 2 vorrangegangenen Chemotherapielinien in der metastasierten Situation • Prä- oder postmenapausaler Status • Mindestens eine nach RECIST auswertbare metastatische Läsion, entsprechend den RECIST Leitlinien Version 1.1., basierend auf lokaler Beuerteilung. • Tumorevaluation nach RECIST Version 1.1 innerhalb von 4 Wochen vor Studienrandomisierung • Alter ≥ 18 Jahre • 12-Kanal-EKG: -QTcF Interval bei der Einschlussvisite < 450 msec -Ruheherzfrequenz 50-90 s/min • Echokardiografischer Nachweis einer linksventrikulären Ejaktionsfraktion (LVEF) ≥ 50% zu Studienbeginn • ECOG Score ≤ 2 • Adäquate Knochenmarksreserve und Organfunktion 14 Tage vor dem Zeitpunkt der Rekrutierung, durch folgende Laborparameter bestätigt: - Absolute Neutrophile ≥ 1500/µL, - Thrombozyten ≥ 100000/µL, - Hämoglobin ≥ 9 g/dL, - ALT (SGPT) ≤ 2.0 × ULN (≤ 3.0 × ULN bei Lebermetastasierung) - AST (SGOT) ≤ 2.0 × ULN (≤ 3.0 × ULN bei Lebermetastasierung) - Bilirubin (gesamt) ≤ 1.5 × ULN (Ausnahme Gilbert's Syndrom) - Kreatinin ≤ 2.0 mg/dl oder 177µmol/L - INR ≤ 1,5 • Unauffällige Laborwerte für: Natrium, Kalium, Kalzium (Ribociclib-Therapie) • Bei Patientinnen im gebärfähigen Alter gilt: Negativer Schwangerschaftstest innerhalb von 7 Tagen vor Randomisierung und sichere Kontrazeption (d.h. einfache oder kombinierte nicht-hormonelle Kontrazeption mit einer Versagerquote < 1% oder komplette sexuelle Abstinenz) während der Behandlungsdauer bis einschließlich 7 Monate nach Einnahmeende der Studienmedikation. **Ausschlusskriterien:** Patientinnen können nicht in die Studie eingeschlossen werden, wenn einer der folgenden Punkte zutrifft: • Anamnestisch bekannte Überempfindlichkeit gegenüber Trastuzumab, Pertuzumab oder Ribociclib

	oder chemisch verwandten Bestandteilen bzw. weiteren Bestandteilen der Medikation • Vortherapie mit mTOR- oder CDK4/6-Inhibotoren. • Zwingende Indikation zur Durchführung einer Chemotherapie • Polyneuropathie (PNP) ≥ 2 für Taxantherapie • ZNS Metastasen • Vorliegen von Erkrankungen oder besonderen sozialen oder psychiatrischen Bedingung, die die adäquate Einschätzung oder Evaluation der Studiendaten gefährden oder die Einhaltung des Studienprotokolls stören oder nach Ansicht des behandelnden Arztes zu einer unverhältnismäßigen Gefährdung der Patientin bei Studienteilnahme führen würde • Progress unter Pertuzumab Therapie • Behandlung mit Pertuzumab innerhalb der letzten 12 Monate • Behandlung mit anderen Prüfsubstanzen während der Studie • Unverträglichkeit gegen Soyalecithin und Erdnüsse • Lebenserwartung < 6 Monate • Manifeste kardiale Vorerkrankungen, einschließlich: • Symptomatische Herzinsuffizenz oder LVEF < 50 % • Therapiebedürftige oder klinisch relevante Arrhythmien, z.B. Vorhoftachykardien mit einem Ruhepuls ≥100/min, relevante ventrikuläre Arrhythmien (ventrikuläre Tachykardie), höhergradiger AV-Block (2° AV-Block Typ 2 [Mobitz 2] oder 3° AV-Block) • behandlungsbedürftige Angina Pectoris • klinisch relevante Herzklappenerkrankungen • Nachweis einer transmuralen Infarzierung im EKG • schlecht kontrollierte art. Hypertonie (z.B. systolisch >180 mm Hg oder diastolisch >100 mm Hg) • jede andere kardiale Begleiterkrankung, die nach Ansicht des behandelnden Arztes zu einer unverhältnismäßigen Gefährdung der Patientin bei Studienteilnahme führen würde • Ruhedyspnoe oder andere Erkrankungen, die eine kontinuierliche Sauerstofftherapie erfordern • Schlecht eingestellter Diabetes mellitus oder Nachweis einer klinisch relevanten diabetischen Vaskulopathie • Bekannte HIV-, Hepatitis B- oder Hepatitis C-Erkrankung • Männlicher Patient • Schwangerschaft oder Stillzeit sowie gebärfähige Patientinnen ohne negativen Schwangerschaftstest in den letzten 7 Tagen vor Studienrandomisierung oder mit unsicheren Verhütungsmethoden • Medizinische oder psychologische Gegebenheiten, die das Verständnis oder die Wiedergabe der

informierten Einwilligung verhindern oder die Beendigung der Studie stören.
- Teilnahme an einer anderen klinischen Studien innerhalb der letzten 30 Tage vor Studienregistration
- Vollständige oder teilweise Geschäftsunfähigkeit

Behandlung:

Patientinnen werden abhängig von der Randomisierung mit Trastuzumab/ Pertuzumab und Chemotherapie oder Trastuzumab/ Pertuzumab (plus Ribociclib nach Inkrafttreten des Amendments) und endokriner Therapie behandelt. Ein Wechsel von Chemotherapie zu endokriner Therapie oder umgekehrt ist nicht erlaubt. Ein Wechsel der Medikation auch innerhalb der Behandlungsarme ist nicht möglich.

Drei Wochen nach Abschluss der Chemotherapie soll mit endokriner Therapie begonnen werden. Spätenstens sechs Wochen nach Abschluss der Chemotherapie, bei guten Laborwerten und unauffälligem EKG, werden die Patientinnen mit einer endokrinen Erhaltungstherapie (plus Ribociclib nach Inkrafttreten des Amendments) behandelt.

Trastuzumab/ Pertuzumab muss vor der Chemotherapie intravenös verabreicht werden.

Empfohlene Dosierung für Pertuzumab:
Initiale Dosis: 840 mg Pertuzumab als intravenöse Infusion über 60 Minuten, d1; für die nachfolgenden Infusionen: 420 mg Pertuzumab als intravenöse Infusion über 30-60 Minuten, q3w

Empfohlene Dosierung für Trastuzumab:
Initiale Dosis: 8 mg/kg Körpergewicht Trastuzumab als intravenöse Infusion über 90 Minuten, d1; für die nachfolgenden Infusionen: 6 mg/kg Körpergewicht Trastuzumab als intravenöse Infusion über 30 Minuten, q3w

Empfohlene Dosierung für Ribociclib:
Ribociclib wird in Form vonTabletten 3 x 200 mg 1-21 d q28d verabreicht.

Empfohlene Dosierung für Chemo- oder endokrine Therapie

Chemotherapie	**Empfohlene Dosierung**
Docetaxel	75 mg/m^2 i.v. d1 q3w

Paclitaxel	Zwei Chemotherapieregimen sind möglich: 90 mg/m^2 i.v. d1, 8, 15 q4w oder 80 mg/m^2 i.v. d1, 8, 15, 22 q4w; Behandlungsdauer mit Paclitaxel im Ermessen des behandelnden Prüfarztes, jedoch empfohlene Mindesttherapiedauer 4 Monate oder bis inakzeptabler Toxizität oder Krankheitsprogression
Capecitabine	2 x 1000 mg/m^2 p.o. d1-14 q3w; Behandlungsdauer mit Capecitabine im Ermessen des behandelnden Prüfarztes. Mindesttherapiedauer 4 Monate oder bis inakzeptabler Toxizität oder Krankheitsprogression.
Vinorelbine	30 mg/m^2 i.v.. d1+d8 q3w; Behandlungsdauer mit Vinorelbine im Ermessen des behandelnden Prüfarztes, jedoch Mindesttherapiedauer 4 Monate oder bis inakzeptabler Toxizität oder Krankheitsprogression
nab-Paclitaxel	125 mg/m² d1, 8, 15 q4w; Behandlungsdauer mit Nab-Paclitaxel im Ermessen des behandelnden Prüfarztes, jedoch Mindesttherapiedauer 4 Monate oder bis inakzeptabler Toxizität oder Krankheitsprogression
Eribulin	1,23 mg/m² i.v. d1, 8 q3w, Behandlungsdauer mit Eribulin im Ermessen des behandelnden Prüfarztes. Mindesttherapiedauer 4 Monate oder bis inakzeptabler Toxizität oder Krankheitsprogression
endokrine Therapie	**Empfohlene Dosierung**
Exemestan	25 mg/d p.o.
Letrozol	2,5 mg/d p.o.
Anastrozol	1 mg/d p.o.
Fulvestrant	500 mg i.m. d1+15+28, dann q28d
Leuprorelin	3,75 mg 1 M Depot s.c. q4w, 11,25 mg 3 M Depot s.c.
Goserelin	3,6 mg s.c. q4w

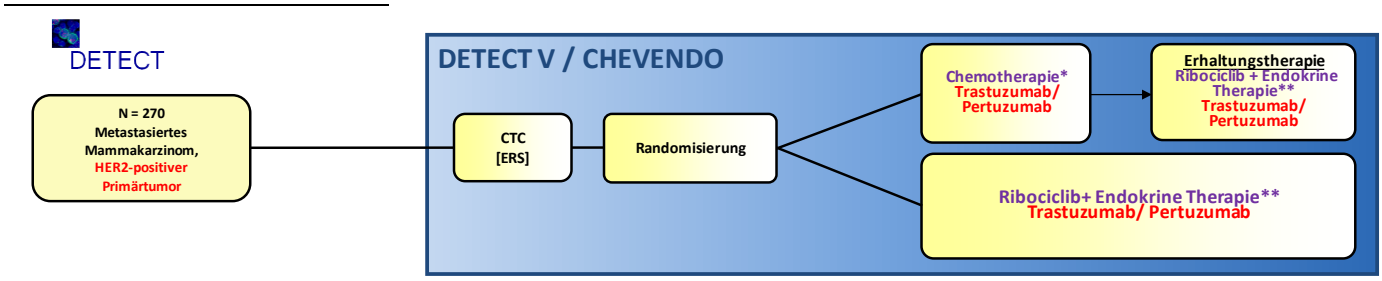
	Dauer der Studienbehandlung: • Abhängig vom gewählten Präparat und dem gewählten Behandlungschema • Abhängig von Tumorprogress, unerwünschter Toxizität sowie weiteren Situationen, die einen Therapieabbruch erfordern • Für Chemotherapie wird eine Mindestdauer von 4 Monaten empfohlen (soweit es nicht medizinische Gründe für einen vorzeitigen Abbruch der Behandlung gibt). Drei Wochen nach Abschluss der Chemotherapie soll mit endokriner Therapie begonnen werden. Spätestens sechs Wochen nach Abschluss der Chemotherapie, bei guten Laborwerten und unauffälligem EKG, werden die Patientinnen mit einer endokrinen Erhaltungstherapie (plus Ribociclib nach Inkrafttreten des Amendments) behandelt. Begrenzt auf die 12-monatige Studienbehandlungsperiode; eine Verlängerung der Behandlung über die Dauer der Studienbehandlungsperiode hinaus ist bei medizinischer Indikation für alle Therapien möglich *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. Alle in der Studienbehandlungsperiode gegebenen Therapien können bei medizinischer Indikation unbegrenzt verlängert werden. Die Studienmedikation wird bis zum Ende der Follow-Up-Phase gestellt.
Patientinnenkollektive, statistische Methoden und Fallzahlberechnung	**Patientinnenkollektive** *Intention to Treat (ITT) Kollektiv:* Alle randomisierten Patientinnen. *Tolerability Kollektiv:* Alle randomisierten Patientinnen, welche die Studienmedikation mindestens einmal erhalten haben und für die mindestens eine Sicherheitsauswertung nach Studienbeginn durchgeführt wurde. *Per Protocol (PP) Kollektiv:* Alle Patientinnen des ITT-Kollektivs, welche weder Ein- noch Ausschlusskriterien verletzt haben und welche nach Studienplan behandelt wurden. Falls notwendig, können modifizierte oder zusätzliche Patientinnenkollektive für weitere spezifische Auswertungen in einem Statistical Analysis Plan (SAP) definiert werden. **Statistische Methoden** In der konfirmatorischen Primäranalyse (sowie den explorativen Analysen zu den beiden sekundären Hauptendpunkten) wird der Anteil an Patientinnen mit während der Behandlungsphase aufgetretenen unerwünschten Ereignissen (definiert nach dem

	modifizierten “adverse event score”) zwischen beiden Behandlungsarmen mit einem χ^2 Test verglichen, wobei die relativen Risiken, das relative Risikoverhältnis sowie die entsprechenden 95% Vertrauens-bereiche berichtet werden. Zusätzlich werden in explorativen Analysen die Vergleiche der Anteile an Patientinnen mit während der Behandlungsphase aufgetretenen unerwünschten Ereignissen zwischen beiden Behandlungsarmen auch für die durch die Stratifizierungsfaktoren vorgegebenen Subgruppen (mit vs. ohne viszerale Metastasen; erste vs. höhere Chemotherapie-Linie; mit vs. ohne vorangegangener Trastuzumabbehandlung; mit vs. ohne vorangegangener Pertuzumabbehandlung) durchgeführt. Für die konfirmatorische Primäranalyse werden alle Patientinnen eingeschlossen, welche nach Inkrafttreten des Amendments (d.h. nach der Hinzunahme von Ribociclib in beide Studienarme) randomisiert worden sind (siehe Rationale der Studie). Entsprechend der zwei sekundären Hauptendpunkte (siehe Rationale der Studie) wird diese Analyse auch für Patientinnen, die vor Inkrafttreten des Amendments in die Studie eingeschlossen worden sind (d.h., Patientinnen, welche kein Ribociclib im Rahmen ihrer Studienbehandlung erhalten haben) und für alle in die Studie eingeschlossenen Patientinnen (unabhängig davon, ob sie vor oder nach Inkrafttreten des Amendments eingeschlossen wurden; ITT und/oder Safety-Kollektiv) durchgeführt. Alle statistischen Analysen welche die sekundären Studienziele betreffen haben nur explorativen Charakter und werden sowohl mit dem gesamten Safety bzw. ITT Kollektiv als auch mit den Subkollektiven der Patientinnen mit und ohne zusätzliche Ribociclib-Behandlung durchgeführt. Der sekundäre Endpunkt qualitäts-adjustiertes Überleben (quality-adjusted survival, QAS) wird mittels der Q-TWiST-Methode (quality-adjusted time without symptoms and toxicity) analysiert (siehe Goldhirsch et al. 1989; Glasziou et al. 1990; Gelber et al. 1993). Alle auf Häufigkeiten bzw. Raten basierenden sekundären Endpunkte und Parameter (ORR, DCR, CR, PR, SD) werden mit Hilfe von absoluten und relativen Häufigkeiten in Häufigkeitstabellen sowie den entsprechenden Vertrauens-intervallen beschrieben. Die entsprechenden Gruppenvergleiche werden mittels geeigneter nicht-parametrischer statistischer Verfahren wie Fisher’s exakter Test, χ^2-Test, oder Cochran-Mantel-Haenszel Test durchgeführt. Progressionsfreies und Gesamtüberleben werden mit der Kaplan Meier Product Limit Methode bestimmt und anhand von Medianen, 95% Vertrauensintervallen und Überlebenskurven beschrieben bzw. dargestellt; Gruppenvergleiche werden mit dem Log-Rank Test durchgeführt. Für multivariate Überlebensanalysen werden geeignete Regressionsmodelle verwendet (z.B. Cox-Regression, logistische Regression).

	Vorhandensein und Anzahl zirkulierender Tumorzellen (circulating tumor cells, CTCs) an verschiedenen Zeitpunkten werden beschreibend dargestellt, und die Änderung der Anzahl CTCs über die Zeit wird mit geeigneten linearen Modellen (z.B. Generalized linear mixed models) untersucht. Zusätzlich sollen verschiedene Maße der CTC Dynamik (basierend auf verschiedenen Schwellenwertkritierien; relative oder absolute Änderungen der CTC-Anzahl) explorativ auf ihre Eignung als prognostische oder prediktive Marker evaluiert werden. Mehr Details zur den statistischen Auswertemethoden werden in einem Statistical Analysis Plan (SAP) dargestellt, welcher vor dem Data Base Lock finalisiert wird. Soweit nicht anders angegeben, werden alle statistischen Analysen mit dem Statistikprogramm IBM® SPSS® Statistics durchgeführt. **Fallzahlberechnung** DETECT V/CHEVENDO ist angelegt als eine zweiarmige, randomisierte Phase III Überlegenheitsstudie. Das primäre Studienziel ist der Vergleich des Anteils an Patientinnen mit unerwünschten Ereignissen (definiert nach dem modifizierten “adverse event score”; evaluiert basierend auf NCI CTCAE Version 4.03) zwischen dem Behandlungsarm mit dualer HER2 gerichteter Therapie plus Chemotherapie und dem Behandlungsarm mit dualer HER2 gerichteter Therapie plus endokriner Therapie (χ^2 Test). Die Fallzahlberechnungen basieren auf der Annahme, dass für Patientinnen mit HER2-positivem metastasiertem Brustkrebs, die mit einer dualen HER2-zielgerichteten Therapie plus Chemotherapie behandelt werden, der Anteil an nach dem modifizierten “adverse event score” definierten unerwünschten Ereignissen 86.3% beträgt (Ergebnisse der CLEOPATRA-Studie, Daten von Roche). Basierend auf dieser Annahme sind mindestens 121 Patientinnen pro Behandlungsarm notwendig, um ein um 20% reduziertes Risiko eines unerwünschten Ereignisses für Patientinnen mit dualer HER2-zielgerichteter Therapie plus endokriner Therapie im Vergleich zu Patientinnen mit dualer HER2-zielgerichteter Therapie plus Chemotherapie nachweisen zu können (90% Power, zweiseitiger Test, $\alpha = 0.05$). Unter der Annahme einer “loss to follow-up” Rate von ca. 10% müssen 270 Patientinnen mit HER2-positivem und hormonrezeptor-positivem metastasiertem Brustkrebs für diese Studie rekrutiert werden. Für das Inkrafttreten des Amendments mit der Hinzunahme des CDK4/6 Inhibitors Ribociclib in beiden Randomisierungsarmen wurde eine separate Fallzahlkalkulation durchgeführt um die statistische Power der Analyse des neuen primären Endpunkts für die Ribociclib-Kohorte zu ermitteln. Hierfür wird angenommen, dass 90 Patientinnen vor Inkrafttreten des Amendments in

	die Studie rekrutiert werden (diese Patientinnen erhalten kein Ribociclib). Dementsprechend wird davon ausgegangen, dass 180 Patientinnen nach Inkrafttreten des Amendments rekrutiert werden und demzufolge Ribociclib erhalten. Basierend auf der Annahme, dass für Patientinnen mit HER2-positivem metastasiertem Brustkrebs, die mit einer dualen HER2-zielgerichteten Therapie plus Chemotherapie behandelt werden, der Anteil an nach dem modifizierten "adverse event score" definierten unerwünschten Ereignissen 86.3% beträgt (siehe oben), ergibt eine Fallzahl von 80 Patientinnen pro Behandlungsarm (180 Patientinnen, die Ribociclib erhalten, "loss to follow-up" Rate von ca. 10%) eine statistische Power von 76% (zweiseitiger Test, α = 0.05) für die Detektion eines um 20% reduziertes Risikos eines unerwünschten Ereignisses für Patientinnen mit dualer HER2-zielgerichteter Therapie plus Ribociclib und endokriner Therapie im Vergleich zu Patientinnen mit dualer HER2-zielgerichteter Therapie plus Chemotherapie (gefolgt von einer Erhaltungstherapie mit dualer HER2 Blockade plus Ribociclib und endokriner Therapie).

Abbildung 6: **Neues Studiendesign nach der Hinzunahme von Kisqali®**



* Capecitabin, Docetaxel, Paclitaxel, Vinorelbin, Eribulin, nab-Paclitaxel
** Fulvestrant, Exemestan, Letrozol, Anastrozol, GnRH-Analoga