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	Dr. med. Fabienne Schochter 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): November 2022 Treatment period end date (LP off treatment): November 2023 Study treatment period: max. 12 months Follow-up end date (LPO): November 2024 Follow up period: max. 24 months until Follow-up end date
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 Kisqali® (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 Kisqali® (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 Kisqali® (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 No longer provided as study medication	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
Additionally for pre- and peri-menopausal women	Recommended Dosing Note: GnRH analogs only in combination with endocrine therapy.

	<table><tr><td>Leuprorelin</td><td>3,75 mg 1 M Depot s.c. q4w, 11,25 mg 3 M Depot s.c.</td></tr><tr><td>Goserelin</td><td>3,6 mg s.c. q4w</td></tr></table> *Duration of study treatment:* • depends on the occurrence of tumor progression, inacceptable toxicity or other criteria for discontinuation but **is limited to max. 12 month study treatment period,** all therapies can be extended beyond the end of the study treatment period in the follow up if medically indicated • 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. *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.