ANTI-HORMONAL MAINTENANCE TREATMENT WITH OR WITHOUT THE CDK4/6 INHIBITOR RIBOCICLIB AFTER 1ST LINE CHEMOTHERAPY IN HORMONE RECEPTOR POSITIVE / HER2 NEGATIVE METASTATIC BREAST CANCER: A PHASE II TRIAL (AMICA)

GBG 97

EudraCT no.: 2017-003667-35

Protocol (Version 3.0 - 19-SEP-2018)

Amendment 1 – 19-SEP-2018

3. Protocol Synopsis

Study Title	**Anti-hormonal maintenance treatment with or without the CDK4/6 inhibitor Ribociclib after 1st line chemotherapy in hormone receptor positive / HER2 negative metastatic breast cancer: A phase II trial**
Study Code	**GBG 97**
EudraCT Number	2017-003667-35
Sponsor	GBG Forschungs GmbH, Neu-Isenburg
Development Phase	Randomized phase II
Background	Dysregulation of the cell cycle is one of the hallmarks of cancer. The cycline dependent kinases are a large family of serine / threonine kinases that have a crucial role in regulating cell cycle progression. Once they are activated by their catalytic partners, the cyclines, they promote cell cycle progression in normal and malignant cells. The cycline dependent kinases 4 and 6 (CDK4/6) and their partner d-type cyclines control transition from G1 to S phase of the cell cycle by phosphorylating the retinoblastoma protein. Strong preclinical evidence has been demonstrated for a synergistic growth inhibitory effect of CDK4/6 inhibition with antiestrogens in hormone-receptor (HR) positive breast cancer cell lines. Palbociclib, an oral small molecule inhibitor of CDK4/6 has been shown to significantly prolong progression free survival (from 10.2 to 20.2 months) in postmenopausal women with metastatic HR-positive / HER2-negative breast cancer when added to letrozole in a randomized phase II and the subsequent phase III study (from 14.5 to 24.8 months; HR=0.58). Treatment was well tolerated with mostly grade 1-2 adverse events with the exception of grade 3 neutropenia, which rarely leads to febrile neutropenia. Ribociclib another CDK4/6 inhibitor is currently evaluated in various disease settings including phase III trials in metastatic breast cancer. The phase III MONALEESA-2 trial has reported a significant improvement in PFS in 1st line metastatic breast cancer when ribociclib was added to letrozole (25.3 vs. 16.0 months; HR=0.57). Albeit the guidelines recommend to use endocrine therapy as the first step in HR-positive/HER2-negative metastatic breast cancer about 30% will receive chemotherapy. At present, no evidence is available about the optimum

	duration of first-line chemotherapy in metastatic breast cancer. Although, a meta-analysis of 11 randomized trials has shown that longer duration of therapy is associated with longer progression-free survival (PFS) and overall survival (OS), the duration of chemotherapy is usually determined by toxicities and patients and physicians´ preferences, resulting in treatment periods of less than 6 months. In contrast, maintenance treatment strategies are standard of care not only in breast but also in lung cancer, colorectal cancer, lymphoma and myeloma. Longer OS and PFS have been demonstrated recently in patients treated with capecitabine and bevacizumab as compared to bevacizumab alone as maintenance treatment after 1st line therapy with a taxane and bevacizumab. Maintenance treatment with anti-hormonal drugs is also an accepted treatment strategy in everyday clinical practice although prospective data are lacking. However, data were presented recently, demonstrating that maintenance treatment with bevacizumab and exemestane was as effective as prolonged therapy with paclitaxel and bevacizumab with better tolerability.
Rationale	Although 1st line chemotherapy is effective in women with HR-positive HER2-negative breast cancer, PFS is usually around 6-8 months and 2nd or 3rd line treatments are by far less effective. Well tolerated maintenance treatments with the potential to prolong PFS and even OS are urgently needed. This study evaluates the impact of the addition of a CDK4/6 inhibitor to an anti-hormonal maintenance treatment of physicians´ choice.
Primary Objective	To evaluate the impact on PFS of an anti-hormonal maintenance therapy after 1st line chemotherapy at the discretion of the investigator (e.g. taxanes, capecitabine, vinorelbine, anthracycline) with or without the CDK4/6 inhibitor ribociclib.
Secondary Objectives	• To evaluate the impact on overall survival and clinical benefit rate • To compare safety between the two arms • To compare treatment compliance between the two arms • To evaluate patient reported outcomes
Tertiary objectives	• To evaluate biomarkers in FFPE and blood (e.g. cyclines, RB expression, p27, p16 expression) in metastatic tissue predicting response to CDK inhibition and endocrine therapy • To evaluate the role of mutations, e.g. *PIK3CA*, *ESR1* in ctDNA

Study Design and Treatment	This is a multicenter, prospective, randomized, open-label, controlled phase II study to test the addition of the CDK4/6 inhibitor ribociclib to anti-hormonal treatment as maintenance therapy in patients with disease control (at least stable disease) after 1st line chemotherapy. Stratification factors for randomization will be: Previous endocrine treatment for metastatic disease (yes vs no) Involved sites (<=2 vs >2) Best response under chemotherapy (response vs stable disease) In both study arms, treatment will be given until disease progression, unacceptable toxicity, or withdrawal of consent of the patient.
Inclusion Criteria	Patients will be eligible for study participation only if they comply with the following criteria: 1. Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements. 2. Female patients. 3. Age ≥ 18 years old. 4. Histologically confirmed HER2-/HR+ locally advanced or metastatic invasive breast carcinoma assessed on the primary tumor and/or on the metastatic lesions (preferred). 5. Willingness and ability to provide archived formalin fixed paraffin embedded tissue block or a partial block from primary surgery and/or tumor or metastasis biopsy, which will be used for further breast cancer research. 6. Maintenance endocrine therapy could have already been started up to 6 weeks before randomization, but after achievement of tumor response or stable disease. 7. Maintenance therapy must be preceded prior to randomization by at least 4 cycles of a mono- or polychemotherapy. Tumor response or stable disease needs to be maintained to allow entry into the trial. Study treatment must start within 8 weeks of the last dose of chemotherapy. 8. Previous therapy with maximum one line of anti-hormonal treatment is allowed.

	9. Previous neoadjuvant/adjuvant therapy is allowed. In case of cancer other than breast cancer, treatment should be completed more than 5 years before study entry. 10. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1. 11. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 4.03 Grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion). 12. The patient must be accessible for scheduled visits, treatment and follow-up. Patients registered on this trial must be treated at the participating center which could be the Principal or a Co-investigator's site. 13. Life-expectancy > 6 months. 14. The subjects need to be either A) of non-childbearing potential (documented postmenopausal or post hysterectomy) or B) childbearing potential with negative urinary pregnancy test (in this case patients need to use highly effective non-hormonal contraceptive).
Exclusion Criteria	1. Uncontrolled/untreated central nervous system lesions. 2. Known severe hypersensitivity reactions to compounds similar to one of the investigational (active substance or peanut, soya or other excipients) and supportive treatment. 3. Inadequate organ function immediate prior to randomization including: – Hemoglobin < 10 g/dL – Absolute neutrophil count (ANC) < 2000/mm³ (< 2.0 x 10^9/L) – Platelets < 100,000/mm³ (< 100 x 10^9/L) – Alanine aminotransferase (ALAT/SGPT) and/or aspartate aminotransferase (ASAT/SGOT) > 2.0 x upper normal limits (ULN). If the patient has liver metastases, ALT and AST should not be ≥5 ULN. – Alkaline phosphatase (ALP) > 2.5 x ULN – Total serum bilirubin > 1.5 x ULN

	– Serum creatinine >1.5 x ULN or estimated creatinine clearance < 60 mL/min as calculated using the method standard for the institution 4. Severe and relevant comorbidity that would interact with the participation in the study. 5. Previous malignant disease being disease-free for less than 5 years (except CIS of the cervix and non-melanomatous skin cancer). 6. Evidence for active infection including wound infections and anamnestic HIV or hepatitis. 7. QTc >450 msec or a family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes. 8. Uncontrolled electrolyte disorders that can compound the effects of a QTc prolonging drug (i.e. hypocalcemia, hypokalemia, hypomagnesemia). 9. Any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.03 grade ≥ 2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism. 10. Other severe acute, uncontrolled or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. 11. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry. 12. Patients treated within the last 7 days prior to randomization with drugs known to be CYP3A4 inhibitors or inducers (see section 11.4) or drugs that are known to prolong the QT interval. 13. Pregnant and lactating women.

Investigational product and formulation	Ribociclib (CDK4/6 inhibitor) 600mg orally (three 200mg tablets) 3 weeks on, 1 week off.
Non-investigational product and formulation	Anti-hormonal treatment of choice (anastrozole/ letrozole/ exemestane/ fulvestrant +/- LHRH analogue for premenopausal women)
Supportive treatment	At the discretion of the treating physician
Primary endpoint	Primary efficacy endpoint is locally-assessed progression-free survival (PFS) defined as the time elapsed between randomization and tumor progression or death from any cause.
Secondary endpoints	**Efficacy endpoints:** • Overall survival (OS) defined as the time elapsed between treatment randomization and death from any cause • Clinical benefit rate (CBR) defined as the proportion of subjects with best response of complete response, partial response, or stable disease for at least 24 weeks **Safety** will be assessed on the basis of adverse events, serious adverse events and adverse events of special interest. Safety by toxicity grades is defined by the NCI-CTCAE version 4.03. **Compliance** will be assessed on the basis of treatment reductions, interruptions and permanent discontinuations with reasons. **Quality of life (QoL)** will be assessed using the General Quality of Life questionnaire (FACT-B), which will be filled in at study entry and every three month thereafter.
Statistical methods Primary endpoint	A modified intent-to-treat (mITT) analysis will be conducted for all patients who started therapy (i.e. patients receiving endocrine therapy alone must have taken their medication at least once after randomization). In addition a per-protocol analysis will be conducted (see section 14.1.2 for definition). Patients lost to follow up or progression-free at the end of the study will be censored at the date of last contact. Patients starting a chemotherapy or targeted therapy after discontinuation of endocrine therapy will be censored at the date of the beginning of the new therapy. PFS curves will be estimated using the Kaplan – Meyer method and compared using a stratified two-sided log-rank test with $\alpha = 0.15$.

	Univariate and multivariate Cox proportional hazards models (full models, without variables selection) will be used to adjust hazard ratios for the given stratification factors. Hazard ratios will be reported together with the 85% and the 95% confidence interval (CI).
Sample Size	We estimate a median PFS of 6 months with maintenance endocrine treatment and a median PFS of 10 months with a maintenance therapy with endocrine therapy plus ribociclib, corresponding to a hazard ratio (HR) of 0.60. Assuming PFS follows an exponential distribution and applying a 2:1 randomization 90 events will be required to give 80% power to detect a HR of 0.6 using a two-sided log-rank test with a type-I-error of 0.15. Assuming a 10% drop-out rate on either treatment arm and a non-uniform enrolment rate of 15 patients per month at the peak, it was estimated that 150 patients will need to be enrolled (a maintenance therapy with endocrine therapy plus ribociclib n=100 versus maintenance endocrine treatment alone n=50). The enrolment period is estimated to be 14 months with a follow-up of about 7 months after the last patient is enrolled.
Statistical methods Secondary endpoints	Analysis of the secondary efficacy endpoints will be based on the mITT set. **Overall survival:** Patients lost to follow up or alive at the end of the study will be censored at the date of last contact. OS curves will be estimated using the Kaplan – Meyer method and compared using a stratified two-sided log-rank test with $\alpha = 0.15$. Univariate and multivariate Cox proportional hazards models (full models, without variables selection) will be used to adjust hazard ratios for the given stratification factors. Hazard ratios will be reported together with the 95% confidence interval (CI). **Clinical benefit rate:** The CBR and the associated two-sided 95% confidence interval will be reported overall and for both treatment arms. CBR rates will be compared between arms using a stratified χ^2-test with $\alpha = 0.15$. Uni- and multivariate logistic regression will be performed (as full models, without variables selection) for the CBR to report odds ratio (OR) with 95% CI and to adjust for the given stratification factors. **Safety and compliance:** The whole modified intent-to-treat set is included into the safety analysis. If a patient has been incorrectly randomized or

	accidentally received the wrong treatment for the whole treatment duration, she will be analyzed according to the actual treatment. Frequencies of patients whose treatment had to be reduced, interrupted or prematurely discontinued will be given for both arms, together with reasons for such modifications. The reason for termination includes aspects of efficacy (i.e. termination due to tumor relapse), safety (i.e. termination due to adverse events) and compliance (i.e. termination due to patient's withdrawal of consent). Reasons for premature termination will be categorized according to the main reason and will be presented in frequency tables. Incidence of adverse events, serious adverse events and adverse events of special interest will be descriptively displayed for both treatment arms. **Quality of life:** The FACT-B questionnaires incorporate various scales, which will be computed and analyzed according to the scoring manual. Details will be given in the statistical analysis plan.
Number of sites	It is planned to conduct the study within approximately 20-30 sites in Germany.
Enrollment Period	Approximately 14 months (Q-I 2018 – Q-II 2019).
Study duration	Approximately 21 months (14 months recruitment + 7 months follow-up)
Follow-up Period	7 months after last patient in (LPI)

GBG 97-AMICA schema: