Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy

"PENELOPE^{B}"

GBG-78 - BIG 1-13 - NSABP-B-54-I

EudraCT No.: 2013-001040-62

FDA IND: 123239

Protocol G (Version 11 - 9th April 2019)

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The following Amendment(s) and Administrative Changes with Administrative letters (DIL) have been made to this protocol since the date of preparation: Protocol A (Version 6-23.09.2013)

Country	Amendment No.	Date of Amendment
Global	Administrative Amendment Protocol G (Version 11 - 9th April 2019) **Summary of changes** Update of GBG Subboard Neoadjuvant, and International Steering Committee members, resp. (chapter 1). Change of International Principal Investigator / Coordinating Investigator (chapter 1). Adding of new position "Unblinded independent statistician" (chapter 1).	9th April 2019
Global	Protocol G (Version 11 - 04th May 2017) **Summary of Changes** Specification of potential outcomes of the efficacy interim analysis (Futility, sample size re-estimation up to a new total number of 1250 patients, efficacy) have been added to statistical section in synopsis, section 11.1 and 15 ff. Rationale: Adaptive design of the trial does allow adjustment of patient number based on outcome of 1st	04th May 2017

	efficacy interim analysis.
	
	New information on Human Pharmacokinetic (PK) Data based on IB 2017 added:
	• Section 6.3.3 updated with further information from clinical trials evaluating PK of Palbociclib
	  ○ no dose adjustment for patients with Asian race required
	• section 6.3.4 - palbociclib does not prolong the QT interval to a clinically meaningful extent at the recommended clinical dose (125 mg QD)
	
	Administrative and corrective changes:
	• Update of steering committee member and study contacts
	• Correction of typo Inclusion criteria #9
	• Alignment of wording of exclusion criterion #13 with inclusion criterion #9
	
	• Table "Schedule of acitivities" :
	  ○ Windows updated for treatment visit and added for "end of treatment" and follow-up visit
	  ○ Wording and timing for disease assements specified
	  ○ Wording for SAE reporting aligned with wording in SAE section 17.7
	  ○ Wording for PK-DDI sampling updated since collection finished
	  ○ ctDNA sampling table corrected
	
	• Procedure for unblinding in case of progressive disease specified in section 12.2
	• Administrative window for IP intake added to section 12.3.3
	• Reporting timelines for pregnancy after end of treatment updated in section 12.7
	• Contraception method wording updated in section 13.1
	• Wording and timing for disease assements aligned in section 13.1 to "schedule of activities"
	• IDMC recommendation regarding frequency of interim safety analysis added to section 15.5.7	

	• Wording for SAE reporting in section 13.1 aligned with wording in SAE section 17.7 • Back-up time points for general Palbociclib-PK sampling added in section 13.3 and closure of PK-DDI sampling comment added in same section	
Global	Protocol E (Version 10 - 12th April 2016) **Summary of Changes:** **Substantial** • Inclusion Criterion #2: Specification for bilaterial breast cancer added • Inclusion Criterion #5: Specification which tissue can be used for central testing added • Inclusion Criterion #6: Specification for bilaterial breast cancer added • Inclusion Criterion #10: Radiotherapy requirements adjusted to standard guidelines • Exclusion Criterion #4: QTc criterion adjusted due to new information in Palbociclib IB versions Feb 2015 and Dec 2015 • Exclusion Criterion #5: Specified to electrolyte disorders in general • Exclusion Criterion #13: Removal of endocrine treatment timing which was a description but not an exclusion criterion. Was replaced with definition of radiotherapy window • Exclusion Criterion #15: Drugs known to prolong QTc interval are no longer considered prohibited due to new information in Palbociclib IB versions Feb 2015 and Dec 2015 • Exclusion Criterion #16: Study entry time was specified as date of randomization. • Endocrine treatment options updated. Patients may now be receiving either tamoxifen or aromatase inhibitor (AI: letrozole, anastrozole, or exemestane). For premenopausal patients, concurrent LHRH agonist use is allowable (section 12.8.1) • Patients may now concurrently receive bisphosphonates or rank ligand inhibitors while	12 April 2016

	on this study if necessary for treatment or prevention of osteopenia or osteoporosis (section 12.5.3) • Safety Monitoring Frequency adjusted to IDMC recommendation in section 15.5.7 • Opthamologic assessment removed due to new information in Palbociclib IB versions Dec 2015 • Optional samples for CTC, RNAlater and Fresh-Frozen tissue removed. • Optional ct-DNA sample collection time-point at detection of progressive disease added • Specification of relevant overdose definition in section 17.5.2 and removal notification requirement for non-relevant overdose **Administrative and corrective changes:** • Updated contact addresses and contacts section • Updated reference data in rationale • Alignment of table "schedule of activities" and tables "assessments and schedules" with current protocol • Updated reference data in section 6.3.7 • Added internet reference for appendix 3 • Labelled appendix 4 as no longer applicable in order to align with updated eligibility criteria • Addition of additional time points for PK-DDI samples in case a sample was missed for a patient. • Specification wording on CRF documentation and signing in section 17.8 and 18.5-	
Global	Protocol D (Version 9 - 09th February 2015) **Summary of Changes:** **Substantial** • Inclusion criteria #5: Clarification for testing in case of bilateral breast cancer • Inclusion criteria #6: Centrally testing possibility extended to core biopsy • Inclusion criteria #12: allows now patients with a CPS-EG Score of 2 if ypN+ to participate	09 Feb 2015

	• Exclusion criteria #15: Proton Pump Inhibitors no longer disallowed • Addition of additional stratification criteria: CPS-EG score 3 vs 2&ypN+ • Update of section 6.3.3 Human Pharmacokinetic (PK) Data • Update of section 12.5.1 Prohibited Medication Proton Pump Inhibitors removed • Update of section 15.5 ff Statistical Analysis due to change of inclusion criteria #12 **<u>Administrative and corrective changes:</u>** • Clarifications / correction of schedule of activities table • Clarification of dose modification schedule in Table 3 • Clarification of endocrine treatment starting points in section 10 and 11.3 • Specification of PK sample set requirements in section 13.3 • Update to section 6.3.3 regarding the use of PPIs • Update of Section 7 rationale of the study • Deletion of "Interim Efficacy Analyses" from section 15.5.1 since already in section 15.5.8 • Update on IDMC compostion – Section 16.1 • Incorporation of French protocol version B (Version 7 – 14 Jun 2014) in order to generate a global document Update of references	
Global	Protocol C (Version 8-06.08.2014) Substantial Amendment Summary of Changes: Prognostic Marker Inclusion Criterion #12 with score CPS-EG, allows now the use of surgical biopsy: … using local estrogen receptor status and grade assessed on core biopsies taken before start of neoadjuvant treatment either / or surgical biopsy. Predictive Marker Inclusion Criterion #5, must be PR positive in residual tissue or with the core biopsy: … (>=1% ER and/or PR positive stained cells). Retreatment (12.3.7) and dose reduction (12.3.8) chapter: Increased clarifications to guidance provided	06.Aug.2014

	based on gained experience in the Palbociclib program. Exclusion Criterion #14 allows now prior neoadjuvant treatment to allow entry patients from ADAPT and similar trials: Prior neoadjuvant treatment is acceptable. Editorial changes to Exclusion criteria: #3 (Curent severe or uncontrolled..) was merged with #9 (Other severe acute..) due to repetition. Better wording of #11 (Pregnancy and lactation….) and #15 not recommended medications Chapter 6.3.3 Human Pharmacokinetik Data, Chapter 6.3.4 QTc Evaluation Data, Chapter 6.3.7 Comination with other endocrine agents and 6.3.8 Long Term toxicity Data were updated with the most recent nonclinical and clinical information. The blood sample for ctDNA was increased from 10 ml to 20 ml. Furthermore occasional text clarifications and typographic errors were corrected. Editorial Amendment to update the protocol Version C with Administrative Letter 5 (DIL), FDA-IND number amended	
Global	Protocol B (Version 7-12.06.2014) Editorial Amendment to update the protocol version B with the Administrative letters 1-4 (DIL) into the protocol, correct typographic errors, update Appendix 10 the Declaration of Helsinki	12.Jun.2014
	Administrative Letter No.	Date of Letter (DIL)
Global	5, Appendix 17, chapter 21.17	21.Jul.2014
Global	4, Appendix 16, chapter 21.16	7.Mar.2014
Global	3, Appendix 15, chapter 21.15	30.Jan.2014
Global	2, Appendix 14, chapter 21.14	14.Jan.2014
Global	1, Appendix 13, chapter 21.13	15.Jan.2014
	Local Amendment No	Date of local Amendment
Korea	Translation into local language	n/a
Spain	Translation into local language	n/a
France	French Appendix introducing visual acuity testing at Baseline, Cyclus 7, EOT	05.Aug.2014

	Local Administrative Letter No	Date of local Amendment
Germany	1 (Global Administrative letter sent to German sites)	28.10.2014

1. ADDRESSES, RESPONSIBILITIES AND SIGNATURES

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2. APPROVAL SIGNATURES

Study Title:

Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy

"PENELOPEB"

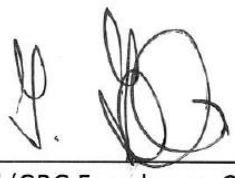
GBG-78 - BIG 1-13

EudraCT no.: 2013-001040-62

FDA IND: 123239

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

Signature: **Date**:



11. April 2019

Prof. Dr. Sibylle Loibl (GBG Forschungs GmbH)
Coordinating Investigator and Representing the Sponsor

Burchardi

11. April 2019

Dr. Nicole Burchardi (GBG Forschungs GmbH)
Study Biostatistician

3. PROTOCOL SYNOPSIS

Study Title	Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy "PENELOPE-B"
Study Code	GBG-78 - BIG 1-13 - NSABP-B-54-I
EudraCT Number	2013-001040-62
Sponsor	GBG Forschungs GmbH, Neu-Isenburg
Development Phase	Phase III
Rationale	About one third of patients with hormone-receptor (HR)-positive, HER2-normal breast cancer and residual disease after neoadjuvant chemotherapy have a substantial risk of relapse. The clinical-pathologic stage – estrogen/grade (CPS-EG)[1] combining clinical stage before neoadjuvant treatment, pathological stage after neoadjuvant treatment, grading and estrogen-receptor status can be used to identify these high-risk patients. The CPS-EG score was additionally validated in 2454 patients with HR-positive/HER2-normal tumors from the German neoadjuvant studies' meta-database. Patients who had a score of 3 or higher or Score 2 and ypN+ disease show a 3-years iDFS of 77% despite adequate local therapy and adjuvant endocrine treatment. Cyclin dependent kinases (CDK), a group of serine/threonine kinases, play a key role in regulating cell cycle progression by interacting with specific cyclin proteins in luminal-type tumors.[2,3] PD-0332991 (palbociclib) is an oral, highly selective inhibitor of CDK4/6 kinase activity that prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 to S phase through blocking retinoblastoma (Rb) phosphorylation.[4] Preclinical studies identified luminal ER subtype, elevated expression of cyclin D1 and Rb protein, and reduced p16 expression as being associated with sensitivity to palbociclib. Final results from a randomized phase II study (Paloma-1/TRIO-18)[5] in 165 postmenopausal, ER+/HER2- metastatic breast cancer patients revealed a progression-free survival of 20.2 months when palbociclib was given in combination with letrozole compared to 10.2 months when letrozole was given alone (HR 0.49 (95% CI 0.32-0.75) (p<0.001). Patients preselected by CCND1 (the gene encoding for cyclin-D1) amplification and/or loss of p16 in the primary tumor did not show different results. Uncomplicated neutropenia (48% grade 3, 6% grade 4), anemia (4% grade 3, 1% grade 4), and fatigue (2% grade 3, 2% grade 4) were the most common grade 3 and 4

	adverse events. The PENELOPE^{B} study is designed to demonstrate that in the background of standard anti-hormonal therapy palbociclib provides superior invasive disease-free survival (iDFS) compared to placebo in pre- and postmenopausal women with HR-positive/HER2-normal early breast cancer at high risk of relapse after showing less than pathological complete response to neoadjuvant taxane- containing chemotherapy. Considering the high risk of recurrence in patients after neoadjuvant chemotherapy and a high CPS-EG score, palbociclib appears to be an attractive option with a favourable safety profile for these patients.
Primary Objectives	To compare invasive disease free survival (iDFS) for palbociclib vs. placebo in patients with residual invasive breast cancer and high CPS-EG score - after neoadjuvant chemotherapy receiving standard adjuvant endocrine therapy for HR-positive/HER2-normal primary breast cancer.
Secondary and other Objectives	Secondary objectives: To compare between the two arms: • iDFS excluding second primary of non-breast cancers • overall survival (OS) • distant disease free survival (DDFS) • locoregional recurrences-free (LRRFS) survival • iDFS per treatment group in patients with luminal-B tumors (as determined by e.g. PAM50 or any other commercially available test at the time of analysis) • compliance and safety according to NCI-CTCAE Version 4.0 • patients reported outcomes • health economic outcomes • to explore drug-drug interaction (DDI) potential for each palbociclib – endocrine combination therapy in a subset of this patient population • to explore correlations between exposure and efficacy and/or safety findings; Other objectives: Scores and markers for their prognostic value in this specific trial setting and their predictive information on the efficacy and/or safety of palbociclib: • pRB immunoreactive score in residual tumor after neoadjuvant treatment • Cyclin D immunoreactive score in residual tumor after neoadjuvant treatment • residual cancer burden (RCB)[6] • clinical response to neoadjuvant chemotherapy (assessed according to chapter 21.1) • incidence and alterations in genes, proteins, and RNAs relevant to

	the cell cycle (eg, CCND1 amplification, CDKN2A deletion), drug targets (eg, CDK 4/6), and tumor sensitivity and/or resistance (Ki67, pRb, tRB, cyclin E, pi3k, p16, and other markers, measured by optimal test available at the time of analysis) in tumor tissues and/or peripheral blood. • Low and high risk groups (defined by Endopredict®, ROR or other any other available test at the time of analysis) • low and high risk groups defined by a standardized image analysis system for Ki67 • circulating tumor DNA (ctDNA)
Study Design and Treatment	This is a prospective, international, multicenter, randomized, double-blinded, placebo-controlled, parallel-group Phase III study comparing the efficacy and the safety of thirteen cycles (1 year) adjuvant treatment with palbociclib versus placebo in high risk (CPS-EG score 3-6 or CPS-EG score 2 and ypN+) patients without pathological complete response after neoadjuvant chemotherapy for hormone-receptor-positive / HER2-normal primary breast cancer. Patient will receive standard adjuvant endocrine treatment after completion of adequate local surgical and radiotherapeutic treatment. Prior endocrine treatment as part of neoadjuvant treatment is acceptable. Adjuvant endocrine treatment might have been started before randomization can be started anytime post-surgery. The study has an adaptive design with two interim analyses including sample size re-estimation and non-binding stopping of the trial due to futility in the first and early stopping of the trial prematurely due to overwhelming efficacy in the second efficacy interim analysis. Due to the adaptive design sample size will be at least 1100 patients. The sample size can be increased to a maximum of 1250 patients depending on the result of the first efficacy interim analysis. Patients will be randomized in a 1:1 ratio to: • Arm A: palbociclib at a dose of 125 mg once daily, day 1 to day 21 followed by 7 days off treatment in a 28-day cycle for thirteen cycles; • Arm B: Placebo of palbociclib once daily day 1 to day 21 followed by 7 days off treatment in a 28-day cycle for thirteen cycles. Randomization will be stratified using block randomization by: • histological lymph node status at surgery (ypN 0-1 vs ypN2-3) • age at first diagnosis (<=50 vs >50 yrs) • centrally measured Ki-67 (>15% vs <=15%) • global region of participating site (Asian vs non Asian) • risk status (CPS-EG Score >=3 vs CPS-EG Score = 2 and ypN+) Due to the prognostic impact of the randomization criterion risk status, randomization to the stratum CPS-EG score =2 and ypN+ will be limited to

	50% of the patients. Palbociclib/Placebo will be given for thirteen 28-day cycles or until diagnosis of invasive local, regional or distant recurrence, diagnosis of secondary malignancy, unacceptable toxicity, or withdrawal of consent of the patient or study termination by the Sponsor, whichever occurs first. Patients in both arms shall receive standard endocrine treatment for at least 5 years.
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. Willingness and ability to provide archived formalin fixed paraffin embedded tissue block or a partial block from surgery after neoadjuvant chemotherapy and from core-biopsy before start of neoadjuvant chemotherapy, which will be used for centralized retrospective confirmation of hormone- and HER2-status and to evaluate correlation between genes, proteins, and mRNAs relevant to the endocrine and cell cycle pathways and sensitivity/resistance to the investigational agents. In case of bilateral breast cancer, tumor tissue of both sides needs to be assessable. 3. Histologically confirmed unilateral or bilateral primary invasive carcinoma of the breast. 4. Residual invasive disease post-neoadjuvant either in the breast or as residual nodal invasion. 5. Centrally confirmed hormone-receptor-positive (≥1% ER and/or PR positive stained cells) and HER2-normal (IHC score 0-1 or FISH negative (in-situ hybridization (ISH) ratio) <2.0 status) assessed preferably on tissue from post-neoadjuvant residual invasive disease or core biopsy of the breast, or if no other tissue is available the residual tumor of the lymphnode can be assessed. In case of bilateral breast cancer hormonreceptor positivity and HER2-normal status has to be centrally confirmed for both sides. 6. Centrally assessed Ki-67, pRB, and Cyclin D1 status assessed preferably on post-neoadjuvant residual invasive disease of the breast, or if not possible, of residual nodal invasion or core biopsy. In case of bilateral breast cancer, tumor tissue of both sides needs to be assessable. 7. Patients must have received neoadjuvant chemotherapy of at least 16 weeks. This period must include 6 weeks of a taxane -containing neoadjuvant therapy (Exception: For patients with progressive disease that occurred after at least 6 weeks of taxane-containing neoadjuvant treatment, a total treatment period of less than 16 weeks is also eligible).

	8. Adequate surgical treatment including resection of all clinically evident disease and ipsilateral axillary lymph node dissection. Histologically complete resection (R0) of the invasive and ductal in situ tumor is required in case of breast conserving surgery as the final treatment. No evidence of gross residual disease (R2) is required after total mastectomy (R1 resection is acceptable). Axillary dissection is not required in patients with a negative sentinel-node biopsy before (pN0, pN+(mic)) or after (ypN0, ypN+(mic) neoadjuvant chemotherapy. 9. Less than 16 weeks interval since the date of final surgery or less than 10 weeks from completing radiotherapy (whichever occurs last) at date of randomization. 10. Completion of adjuvant radiotherapy according to standard guidelines (e.g. AGO Mamma, NCCN) is strongly recommended. If radiotherapy is not performed the reason for this needs to be documented in the eCRF. 11. No clinical evidence for locoregional or distant relapse during or after preoperative chemotherapy. Local progression during chemotherapy is not an exclusion criterion. 12. A clinical-pathologic stage – estrogen/grade (CPS-EG) score of ≥3, or score 2 if nodal status at surgery is ypN+, calculated using local estrogen receptor status and grade assessed on either core biopsies taken before start of neoadjuvant treatment or surgical specimen (see chapter 21.1). 13. Age at diagnosis at least 18 years. 14. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (see Appendix 21.2). 15. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 4.0 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion). 16. Estimated life expectancy of at least 5 years irrespective of the diagnosis of breast cancer. 17. 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.
Exclusion Criteria	1. Known severe hypersensitivity reactions to compounds similar to palbociclib or palbociclib/placebo excipients or to endocrine treatments. 2. Inadequate organ function immediate prior to randomization including: Hemoglobin <10g/dL (100g/L); ANC < 2000/mm³ (< 2.0 x 10^9/L); Platelets <100,000/mm³ (< 100 x 10^9/L); AST or ALT >1.5 x upper limit of normal (ULN); alkaline phosphatase > 2.5 x ULN, total serum bilirubin > 1.25 x ULN; serum creatinine >1.25 x ULN or estimated creatinine clearance < 60 mL/min as calculated using the method standard for the institution; severe and relevant co-morbidity that would interact with

	the participation in the study 3. Evidence for infection including wound infections, Human Immunodeficiency Virus (HIV) or any type of Hepatitis 4. QTc >480 msec 5. Uncontrolled electrolyte disorders (eg, hypocalcemia, hypokalemia, hypomagnesemia). 6. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.0 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. 7. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection. 8. Prior malignancy (including invasive or ductal *in-situ* breast cancer) within 5 years prior to randomization, except curatively treated basal cell carcinoma of the skin and carcinoma in situ of the cervix. 9. Current severe acute or uncontrolled chronic systemic disease (e.g. diabetes mellitus) 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. 10. Recent (within the past year) or active suicidal behavior. 11. Pregnancy or lactation period. Women of childbearing potential must implement adequate non-hormonal contraceptive measures (barrier methods, intrauterine contraceptive devices, sterilization) during study treatment and for 90 days after discontinuation. A serum pregnancy test must be negative in premenopausal women or women with amenorrhea of less than 12 months. 12. Major surgery within 2 weeks prior to randomization. 13. 10 weeks or more have passed since completion of radiotherapy at day of randomization and 16 weeks interval since the date of final surgery have passed. 14. Prior treatment with any CDK4/6 inhibitor. 15. Patients treated within the last 7 days prior to randomization and/or concurrent use of drugs known to be strong CYP3A4 inhibitors or inducers (see appendix 21.3) 16. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to randomization. 17. Male patients.
Investigational product and	Palbociclib/placebo at a dose of 125 mg will be administered orally once a day at the same day time for 21 days followed by 7 days off treatment of

formulation	every 28-day cycle. A total of thirteen 28-day cycles palbociclib/placebo capsules should be administered together with endocrine treatment. Patients should take Palbociclib/placebo with food.
Non-investigational product and formulation	Current treatment guidelines recommend adjuvant endocrine treatment for 5 to 10 years after surgery for patients with hormone-receptor-positive disease. Adjuvant endocrine treatment might have already started before the patient enters the study. Patients may be receiving either tamoxifen or aromatase inhibitor (AI: letrozole, anastrozole, or exemestane). For premenopausal patients, concurrent LHRH agonist use is allowable. PK-DDI sampling was done for patients receiving Tamoxifen or Gosereline+Tamoxifen or Anastrozole as endocrine treatment (collection closed in meantime).
Analysis populations	Randomized patients consist of all patients who have given their written informed consent and for whom there is confirmation of successful allocation of a randomization number through the web-based data collection interface. **Intent to treat (ITT) efficacy population**: all randomized patients (including those not starting treatment). This population provides the basis for the main efficacy analyses. Patients will be analyzed according to the treatment group they were randomized to. **Evaluable patients (EP) efficacy population**: subset of the ITT population, this population includes all treated patients with at least 80% of the planned number of doses of palbociclib/placebo. This population is for supportive efficacy analyses. Patients will be analyzed according to the treatment group they were randomized to. **All randomized and treated patients safety (SP) population**: all randomized patients (excluding those not starting treatment). Patients will be analyzed according to the treatment actually received. This is the only population for all safety analyses. **Translational Research sub-study population:** a subset of randomized and treated patients with available molecular-biological parameters before first study drug administration. All analyses using this population will be based on the treatment received.
Sample size calculation	Sample size was determined based on the analysis of the primary endpoint, iDFS. The sample size was calculated based on the following assumptions: • Time to iDFS event follows an exponential distribution. • 3-year iDFS rates for placebo arm and for the palbociclib arm are 0.77 and 0.836, respectively. The rates are equivalent to a HR (palbociclib/ placebo) of 0.685.

	Based on these assumptions, a minimal number of 255 iDFS events will be required to give 85% power to detect a HR (palbociclib/ placebo) of 0.685 at the 0.05 significance level (2-sided) on iDFS using a stratified log-rank test. Assuming time to dropout follows exponential distribution with a common hazard rate (0.04383 subjects per year) for both arms. Applying a 1:1 randomization and a non-uniform enrollment rate of 40 subjects per month at the peak, it was estimated that 1100 subjects will need to be enrolled. The total enrollment period is estimated to be 3.6 years. The final analysis will take place when 255 iDFS events are observed which is estimated to occur about 6.5 years after first patient. Power calculation is also done for the secondary endpoint of iDFS excluding second primary of non-breast cancer. Assuming that not more than 15% of iDFS events are second primary of non-breast cancer, there is 79% power to detect statistical significance between the 2 arms with a 2-sided significance level of 0.05.
Safety Monitoring	Safety interim analysis (SIA) reviewed by the IDMC have a special focus on safety and reasons for treatment discontinuations (including progressive disease) and are scheduled regarding the number of patients having completed 2 cycles of treatment or discontinued study treatment prematurely: after the first 25 patients, two more SIAs after approximately further 50 patients each, then after further 150 patients and whenever the next 300 patients have completed 2 cycles or discontinued study treatment prematurely. SIA frequency may be adjusted due to the IDMCs recommendations. In subsets of at least 24 evaluable patients each starting with the combination of palbociclib and tamoxifen, palbociclib and anastrozole, and palbociclib and goserelin and tamoxifen plasma PK samples will be collected to explore DDI between palbociclib and the combination drug. No significant DDI between Palbociclib and Letrozole were observed and no samples need to be collected to explore DDI for the Letrozole combination. Review of the PK data will be done by the IDMC once all planned PK samples from the complete subset of 24 measurable patients of each assessed combination have been analyzed. The study will continue while PK analysis and data review are ongoing. The PK analysis and DDI assessment will require unblinded analysts, details regarding the unblinded analysis and the prospective plan for how the blind will be maintained during this process for all study team members can be found in the PK unblinding plan. Details of the analysis (along with other safety data included in the early safety review) will be provided in the IDMC charter. The IDMC will review the data from the early safety lead-in as soon as available in an ad-hoc meeting.
Statistical Analyses	Primary efficacy endpoint is invasive disease-free survival (iDFS) which is defined according to Hudis[7] as the time period between randomization and

Analysis of Primary Endpoint	first event (ipsi- or contralateral invasive in-breast or loco-regional recurrence, distant recurrence, death from breast cancer, death from non-breast cancer cause, death from unknown cause, invasive contralateral breast cancer, second primary invasive cancer (non-breast)). The primary analysis for iDFS will be the comparison between treatment arms in the ITT population with a 2-sided stratified log-rank test at the overall significance level 0.05. The factors used in the stratified log-rank test will be histological lymphnode status at surgery (ypN 0-1 vs ypN 2-3), age at first diagnosis (<=50 vs >50 yrs), Ki-67 (>15% vs <=15%), and risk status (CPS-EG score >= 3 vs. CPS-EG score = 2 and ypN+). Global region will not be included. The nominal significance level for the final analysis of iDFS is 0.0463 because of the two planned interim analyses. In addition, iDFS curve will be estimated in each treatment arm using the Kaplan-Meier method. Cox regression model stratified by the factors used in the stratified log-rank test will be used to estimate the treatment hazard ratio. The iDFS rates at 3 years will also be estimated for each arm. **Final efficacy analysis** Final analysis of the primary endpoint and secondary efficacy endpoints (except for OS) will be conducted when the target number of iDFS events for the final analysis have been observed. The minimum number of iDFS events is 255. Due to the adaptive design of the trial this number can be increased to a maximum of 290 iDFS events depending on the result of the efficacy interim analysis. The final analysis is estimated to be performed approximately 6.5 years after first patient randomized.
Efficacy Interim Analyses:	Two efficacy interim analyses (EIA) will be performed in the study. O'Brien – Fleming type stopping boundaries based on the Lan-DeMets spending function will be applied. Futility criteria are not used to calculate the nominal alphas (non-binding method) in order to control the overall Type-I-error. The objectives of the first EIA will be: • To re-estimate the sample size. • To assess safety, including any unexpected toxicity. • To allow for early stopping of the trial due to futility. The objectives of the second EIA will be: • To assess safety, including any unexpected toxicity. • To allow for early stopping of the trial due to futility. • To allow for early stopping of the trial due to overwhelming efficacy. The first EIA was originally planned to be performed after the first 85 events (1/3 of the total events) have occurred or prior to the last patient randomized to allow for the continuation of the enrollment in case of SSR. According to an estimation in February 2017 the planned fraction of events

would have occurred one month after last patient randomized. It was estimated that approximately two months are required to perform the EIA and to implement potential changes. Therefore, the EIA is scheduled to be performed in April 2017.

The second EIA will be performed on the basis of 2/3 of the total events. It was estimated that 2/3 of 255 events (170 events) will have occurred <5 years from the first patient randomized. In case of sample size re-estimation, 2/3 of 290 events (194 events) must have been documented, which is estimated to have occurred 5.1 years from first patient randomized.

The unblinded results of the EIA will be provided to the IDMC to receive recommendation regarding the efficacy interim analysis' objectives. All staff at GBG will remain blinded to the treatment allocation of the patients with exception of the independent statistician (unblinded statistician).

The following table displays the decision rules regarding the objectives of the two EIA and the final analysis.

Analysis	Time / Information Fraction	Number of events min/max	Futility (HR)	Sample size re-estimation	Efficacy (α-level)
1st EIA	April 2017	67	≥1.0	Yes	<0.0002
2nd EIA	2/3	170/194	≥0.90	No	<0.0120
FA*	3/3	255/290	N/A	N/A	<0.0463

* Final Analysis

The actual nominal α levels for the EIA and for the final analysis will depend on the fraction of total events occurred at the time of analysis, in order to control the overall type I error for the endpoint of iDFS.

At EIA statistical hypothesis tests will be performed only for the primary efficacy parameter, iDFS. The secondary endpoint of iDFS excluding second primary of non-breast cancer will also be taken into consideration when performing sample size re-estimation (SSR).

Cui, Hung and Wang [8] method will be used for adaptive sample size modification. The decision about SSR will be made on the basis of the favorable zone concept by Mehta and Pocock[9]. In case the conditional power calculated on the basis of the efficacy interim analysis' treatment effect fell in the favorable zone, increase of sample size to the maximum of 1250 patients and increase of the number of iDFS events to the maximum of 290 events is planned. The definition of the favorable zone is only laid down in the addendum to the IDMC charter and must be kept secret to avoid "reverse engineering" of the treatment effect.

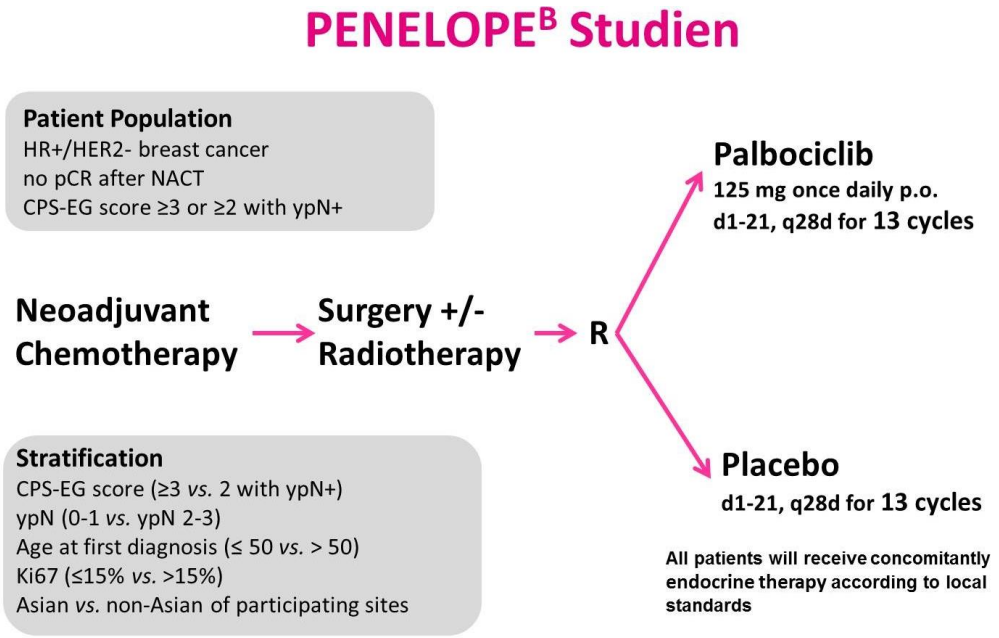
Analysis of Secondary Efficacy

Secondary efficacy endpoints are:

- iDFS excluding second primary of non-breast cancers

Endpoints	• overall survival (OS) • distant disease free survival (DDFS) • locoregional recurrences-free (LRRFS) survival • iDFS per treatment group in patients with luminal-B tumors as determined by PAM50. Overall survival (OS) is defined as the time period between randomization and death of any cause. An interim OS analysis will be conducted at the time of final iDFS analysis and final OS analysis will be conducted at a later time after the final analysis for iDFS endpoint. Details will be described in Statistical Analysis Plan. Locoregional recurrences-free survival (LRRFS) is defined as the time period between randomization and diagnosis of any loco-regional (ipsilateral breast (invasive or DCIS), local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer or death due to any cause whichever occurs first. Distant disease free survival (DDFS) is defined as the time period between randomization and diagnosis of any distant recurrence of disease, any second primary invasive cancer (non-breast) or death due to any cause whichever occurs first. LRRFS and DDFS will be analyzed at the time of final iDFS analysis. Time-to-event curves will be estimated using the Kaplan-Meier method and compared between 2 arms with a two-sided stratified log-rank test. Univariate Cox-proportional hazards model will be used to calculate hazard ratios for the overall population as well as for subgroups predefined by the stratification factors. Multivariate Cox-proportional hazards model will be performed for event free data, to adjust for all stratification factors, as well as clinical stage before neoadjuvant chemotherapy, pathological stage after neoadjuvant chemotherapy, and grade.
Analysis of Other Secondary Endpoints	*Tolerability and Safety:* Descriptive statistics for the 2 treatments will be given on the number of patients whose treatment had to be reduced, delayed or permanently stopped. The reason for termination includes aspects of efficacy (e.g. termination due to tumor progression), safety (e.g. termination due to adverse events) and compliance (e.g. 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. Safety by toxicity grades will be defined by the NCI-CTCAE v4.0. *Patients reported outcome* and health economic analyses: data will be captured using the following questionnaires: the EORTC QLQ-C30, the breast cancer module QLQ-BR23, QLQ fatigue, GAD7 patient self-rating mood scale and the EQ-5d instruments. Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of absolute scores and their changes from baseline will be summarized at each assessment time point for

	the 2 treatment arms. Only patients with a baseline assessment and at least one post-baseline assessment will be included in this analysis. Repeated-measures mixed-effects models will be used to explore the treatment effect changes over time and treatment-by-time interaction. *Translational research*: Exploratory analyses will be performed to identify possible relationships between biomarkers and iDFS and OS. Patients with missing biomarker data will not be included in the respective analysis	
Number of sites	Approx. 300 sites are necessary to recruit approximately 40 patients per month at full speed recruitment. Annual recruitment per site has to be 3.1- 3.6 patients in average, which requires annual neoadjuvant treatment in at least 10 patients of all breast cancer subtypes (35% uptake rate).	
Study Timelines **- original design** **(after sample size re-estimation)**	First patient in: Last patient in First efficacy interim analysis: Second efficacy interim analysis: Final iDFS (and interim OS) analysis: Final OS analysis:	QI 2014 QIII 2017 April 2017 QI 2019 (QII 2019) QIII 2020 QIII 2023
Study duration	QIV 2013 - QIII 2020. No interventional procedures after final iDFS (and interim OS) analysis.	



SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures and Assessments (Section 13) for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

Penelope Schedule of Activities	
I: Routine assessments prior to study entry (Prescreening, Prior to any protocol investigations or procedures**)**	
Imaging test for staging <13 Months	**Breast ultrasound(<13 month) and either bilateral mammography (< 13 months) or bilateral breast MRI (<13 months) data needs to be available . For women treated with mastectomy only imaging data of contralateral breast is required ; for women with bilateral mastectomy an imaging assessment as recommended per national guidelines should be available.** Other instrumental examinations only in case of symptoms suspicious for locoregional or distant relapse. Reports of these examinations within <13 month year prior to enrollment must be available then. Bone scan, CT, MRI, and/or PET-CT scans may be performed as clinically indicated according to the investigator.
Less than 16 weeks prior to randomization	**Surgery (breast-conserving surgery or ablation) excising the initial tumor bed. Subsequent secondary surgical interventions do not count regarding this time interval. All surgery reports** and all pre- and postneoadjuvant histopathology reports including information on the components of residual cancer burden (RCB) (primary tumor bed area, overall cancer cellularity (%), percentage of cancer that is in situ disease, number of positive nodes, diameter of largest metastases) have to be provided.
Less than 10 weeks prior to randomization	**Completion of radiotherapy after surgery** according to guidelines (IORT allowed). Adequate radiotherapy reports including information of time period of radiotherapy, irradiated region and dose per region, dose per day have to be provided

Protocol Activity	Screening	Active Treatment Phase [a] – (1 cycle = 28 days)			End of Treatment / Withdrawal of treatment [c]	Post-Treatment Follow-Up according to ASCO-guidelines [d]	
		Cycles 1 and 2		Cycles 3-13			
Study Day	Within 30 days prior to randomization unless specified otherwise	Day 1 [b]	Day 14	Day 1		Year 2-5 twice a year (+/-14d)	Thereafter until end of study yearly (+/- 14d)
*Time Window for procedures if required due to administrative reasons		+/-2 days*	+/-2 days*	+3 days *	(+3 days for EOT)		
	1 visit	11 visits in total during active treatment			1 visit	site visit, written or tel contact	
Clinical Documentation/Clinical History							
Written Informed Consent Process [e]	before any study related procedure						
History including diagnosis of breast cancer, menopausal status, general medical history including cardiac history and allergy, concurrent illness, response to neoadjuvant therapy CPS-EG [f]	X						
Concomitant Medications/Clinical History [s]	X	Cycle 1, 2, 3, 5, 7, 9, 11,13			X	X	
ECOG Performance Status	X	Cycle 1, 2	Cycle 1, 2	Cycle 3, 4, 5, 7, 9, 11, 13	X		
Physical Examination/Vital signs [l]	X	Cycle 1, 2 b	Cycle 1, 2	Cycle 3, 4, 5, 7, 9, 11, 13	X		
Drug Compliance and dispensing [q]		◄ ►, dispensing Cycle 1, 2,3,4,5,7,9,11,13					
Adverse Event Reporting [r]		X	X	X	X		
Laboratory							
Hematology [m] (Information on hematology lab results [g m)]	<8 days	Cycle 1, 2	Cycle 1, 2	Cycle 3, 4, 5, 6,7, 8,9, 10,11, 12 and 13 and if clinically indicated	X		
Blood chemistry with liver function tests [m]	<8 days	Cycle 1, 2		Cycle 3, 7, 11	X		
HbA1C [y]	X			Cycle 3,7,11	X		
Serum pregnancy test (if applicable) [m]	<14 days	(X)					

Protocol Activity	Screening	Active Treatment Phase [a] – (1 cycle = 28 days)			End of Treatment / Withdrawal of treatment [c]	Post-Treatment Follow-Up according to ASCO-guidelines [d]	
		Cycles 1 and 2		Cycles 3-13			
Study Day	**Within 30 days prior to randomization unless specified otherwise**	**Day 1 [b]**	**Day 14**	**Day 1**		**Year 2-5 twice a year (+/-14d)**	**Thereafter until end of study yearly (+/- 14d)**
***Time Window for procedures if required due to administrative reasons**		**+/-2 days***	**+/-2 days***	**+3 days ***	**(+3 days for EOT)**		
	1 visit	**11 visits in total during active treatment**			**1 visit**	**site visit, written or tel contact**	
SH and E2 in patients aged <55 with history of hysterectomy	X						
Cardiac Monitoring							
12 Lead ECG [n]	X		cycle 1				
Biomaterials							
Liquid biomaterial samples [i]	X			Prior to Cycle 7	X		
Full blood for SNP (pharmacogenomic blood sample) [h]	X						
Pharmacokinetics for all patients [j]			predose Cycle1 Day 14 and Cycle 2 Day 14				
Tumor Tissue [k]	from surgery and core biopsy for central testing of biomarkers used for stratification after ICF signature	In case of disease progression according to the current guidelines from the metastatic lesion					
Disease Assessment							
Clinical disease assessment, relapse and survival status, imaging [v]		Cycle 7 X			EoT X	At least yearly X	
Other Investigations: thoracic or abdominal CT / MRI, bone scans, x-rays, biopsies and others [o]	In case of symptoms suspect for disease progression or as clinically indicated						
PRO / Health Economics							
General Quality of Life (Qol) questionnaire (EORTC-QLQ-C30) [t]	<14d				X	X	

Protocol Activity	Screening	Active Treatment Phase [a] – (1 cycle = 28 days)			End of Treatment / Withdrawal of treatment [c]	Post-Treatment Follow-Up according to ASCO-guidelines [d]	
		Cycles 1 and 2		Cycles 3-13			
Study Day	Within 30 days prior to randomization unless specified otherwise	Day 1 [b]	Day 14	Day 1		Year 2-5 twice a year (+/-14d)	Thereafter until end of study yearly (+/- 14d)
*Time Window for procedures if required due to administrative reasons		+/-2 days*	+/-2 days*	+3 days *	(+3 days for EOT)		
	1 visit	11 visits in total during active treatment			1 visit	site visit, written or tel contact	
Qol breast cancer questionnaire (EORTC-QLQ-BR23) [t]		Cycle 1, 3, 5, 7, 9, 11 (+/-2 days cycle 1,3) (+/-7 days thereafter)					
Fatigue questionnaire (EORTC QLQ FA-13 Fatigue) [t]							
Mood questionnaire (GAD7) [t]							
Health economics questionnaire (EuroQol (EQ)-5D) [t]							
Use of medical resources (Patient diary)							
Study Treatment							
Randomization after all baseline documentation entered and CPS-EG score calculated	X						
Palbociclib or placebo dosing [w; a]		◄--►[w] Once Daily on Day 1 to Day 21of each Cycle followed by 7 days off					
Endocrine treatment [x]	Prior endocrine treatment acceptable. Adjuvant endocrine treatment can be started anytime post-surgery.	at least 5years					

a	**Active Treatment Phase:** All assessments should be performed prior to dosing with study medications on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers.
b	**Cycle 1/Day 1:** Blood chemistry, hematology, 12-lead ECG and physical examination are not required if acceptable screening assessment was performed within 7 days prior to randomization.

c	**End of Treatment/Withdrawal:** Assessments have to be done at End of Treatment (EOT) visit. End of Treatment is defined as **30d after last intake** of IP. If a laboratory assessment is done after D1 of of cycle 13 but before EOT visit, it needs to documented as additional lab assessement in the eCRF for cycle 13.
d	**Post Treatment Follow-up:** Patients who discontinue study treatment for any reason other than objective disease progression or death will continue to have tumor assessments performed according to ASCO guidelines. See Tumor Assessment Requirements Flowchart for details. For patients who discontinue study treatment due to objective disease progression, survival data (i.e., patient status, onset and type of new anticancer therapy will still be collected approximately every 6 months (+/- 14 days) from the last dose of study treatment. See section 13.8 on details of documenting imaging, first palliative treatment and clinical disease assessment.
e	**Informed Consent:** Informed consent may be obtained greater than 30 days before randomization; however, must be obtained prior to any protocol specific assessments.
f	**History (Medical/Oncological):** To include information on prior anticancer treatments. The clinical-pathologic stage – estrogen/grade (CPS-EG) score and grade assessed according to Appendix 21.1). Baseline tumor therapy related signs and symptoms will be recorded at baseline visit together with the Medical history prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency. Patients should have recovered from toxic effects of prior treatment, see inclusion criterion 15.
g	**Information based on external results** at Day 1 of Cycles 6, 8, 10 and 12 are allowed per protocol. However investigator must ensure repeated site labs are provided if external labs are significant and would require a dose reduction based on the CBC count and as per the investigator's discretion. See footer m (Hematology) and Table 3 (Dose modifications) for details.
h	**Retained Pharmacogenomic Blood Sample:** A 10 ml full blood sample for SNP (whole blood collection optimized for DNA analysis) will be collected from all patients, unless prohibited by local regulations, at the screening (or at any timepoint after randomization) visit to be retained for potential pharmacogenomic analyses (SNP) related to drug response. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.
i	**Liquid biomaterial samples**: Two de-identified blood samples (10 ml full blood for serum and 10 ml full blood for plasma) will be collected from all patients at baseline, prior to Cycle 7 and at the end of treatment, unless prohibited by local regulations. The baseline samples must be drawn prior to the first dose of study drug (Cycle 1, Day 1). (see biomaterial management manual for additional details).
j	**Pharmakokinetics**: Mandatory plasma PK samples must be drawn predose on Day 14 of Cycle 1 and Cycle 2 for all patients.
k	**Tumor Tissue for Biomarker Assessments:** Tumor tissue is required for patient participation, and patients must agree to provide tissue from the metastatic or recurrent site at the time of study entry. For the purpose of eligibility, documentation of ER-positive and/or PR-positive tumor and HER2 negative tumor will be performed based on local results utilizing an assay consistent with local standards. For retrospective biomarker assessments, archived formalin-fixed paraffin embedded (FFPE) specimen will be collected. Every effort should be made to collect a tumor biopsy from the site of progression. Tissue samples from all patients will be used for additional biomarker analyses. Details on preparation of these samples including processing, storage, and shipment will be provided in the biomaterial management manual. .
l	**Physical Examination /Vital signs:** A full physical examination including an examination of all major body systems (palpation of breast/chest wall, axillae, supra- and infraclavicular region), height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening. Symptom-directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.

m	**Laboratory tests:** Hematology includes hemoglobin, WBC, absolute neutrophils, platelet count. Acceptable Blood Chemistry and Hematology Labs must be provided prior randomization (< 8 days prior randomization). Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, serum creatinine, and albumin. Additional hematology/chemistries panels may be performed as clinically indicated. Laboratory assessments will be performed whenever possible by the same laboratory ("site lab"). The exception are hematology labs on Day 1 of Cycles 6, 8, 10 and 12 which can be done at any laboratory conveniently located for the patient and if accepted per local EC/IRB with protocol approval. Results have to be sent immediately to the site for review. Abnormal external lab results (neutropenia <1000/mm³, thrombocytopenia <50.000/mm³ or anemia grade ≥3) obtained on those dates and at a lab different from the site lab, must be repeated at the site lab within 2 days (=extra, but clinically indicated hematology lab), and the Investigator must immediately determine the impact on study drug dosing and further medical management of the patient based on site lab results (See Table 3 Dose modifications). Serum pregnancy test for women of childbearing potential (<14 days prior randomization). A serum pregnancy test must be negative in premenopausal women or women with amenorrhea of less than 12 months. Testing may be repeated as per request of IRB/IECs or if required by local regulations.
n	**12-Lead ECG including automated calculation of PR interval, QT interval, RR interval, and QRS complex:** To be performed during screening, Day14 Cycle1 and as clinically indicated.
o	**Other Investigations:** Thoracic or abdominal CT / MRI, bone scans, x-rays, biopsies and others in case of symptoms suspect for disease progression or as clinically indicated.
q	**Drug Compliance and dispensing:** IWRS is used for IP dispense. Palbociclib, placebo bottle(s) including any unused medication will be returned to the clinic for drug accountability. Drug accountability will be performed after completion of intake for a cycle and prior to dispensing new drug supply for the next cycle(s) and prior dispensing drug for a dose reduction. Starting with Cycle 5 drug compliance will be documented retrospectively by the site. Patient needs to be advised to start a new bottle with each cycle.
r	**Adverse Events:** The worst grade for each AE in each cycle will be documented. For SAEs, the active reporting period begins from the time that the patient took the first dose of IMP and including 30 calendar days after the last administration of the investigational product. Following the active safety reporting period, newly occurred serious adverse reactions (SARs) have to be documented on the SAE form (e-CRF MedCodes) and have to be submitted to the Sponsor within 24 h after becoming aware of the event. Serious adverse events occurring to a patient after the active reporting period has ended (=post treatment follow up) have to be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor. AEs (serious and non serious) should be recorded on the CRF from the time the patient has taken at least one dose of study treatment through last patient visit.
s	**Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 30 days prior to randomization and up to 28days after the last dose of study treatment. Entries in the patient diary can be used as Medical resources in the post-treatment follow up.
t	**Patient Reported Outcomes Assessments:** All self-assessment questionnaires should be completed by the patients while in the clinic. However they can be posted home (< 14 days), especially during post-treatment follow-up. Interviewer administration in clinic may be used under special circumstances.
u	**Survival Follow-Up:** After discontinuation of study treatment, post-study survival status (including start and type of post-study anticancer therapies) will be collected every 6 months (±14 days) from the last dose of study treatment. Telephone contact is acceptable for visits when no imaging is required..
v	**Imaging (mammograph or MRI):** Imaging should be performed at Cycle 7 and EOT. During follow-up, imaging tests for should be performed according to national guidelines but at least once a year. In patients with mastectomy only contralateral mammography / MRI is required; patients with bilateral mastectomy should be assessed as per national guidelines recommended imaging examination.

w	**Palbociclib or Placebo dosing:** To be taken orally once daily from Day 1 to Day 21 (21 days) of every 28-day cycle. Patients will be required to return all bottles of palbociclib/placebo as well as the completed patient diary at the beginning of each second cycle for drug accountability. Every patient should complete 13 cycles. See details for administration chapter 12.3.3, for recommended dose modifications chapter 12.3.5, for dose interruptions chapter 12.3.6, for dose delays chapter 12.3.7 and for dose reductions chapter 12.3.8.
x	**Endocrine treatment (required for all study patients):** While on study, treatment will continue as per local standard of care. Generics are allowed, if available.
y	**HbA1c measurements** can be done at a local laboratory convenient for the patient. In case of an abnormal value, please refer the patient to a diabetologist or a diabetes nurse for further diagnostic tests and to introduce medication if necessary (which has to be reported on the concomitant medication CRF).

Collection of the following samples is optional and encouraged:

	screening	before cycle 7	EOT	Whithin 4 weeks of detection of progressive disease
ctDNA [1]	2x 10 ml	2x 10 ml	2x 10 ml	2x 10 ml

1 Liquid biomaterial samples: One de-identified blood samples (20ml plasma for ctDNA) will be collected from patients who gave additional consent for blood sampling of ctDNA at baseline (latest before 1st dosing with IP), prior to Cycle 7, at the end of treatment and when progressive disease was detected, unless prohibited by local regulations. The baseline samples must be drawn prior to the first dose of study drug (Cycle 1, Day 1). (See biomaterial management manual for additional details.). If a baseline sample is missed during screening it should be collected after randomization before first patient dosing at the latest.

2 The samples must be frozen immediately at -20°C to -80°C and stored at the center until pick up by a courier service.

For a subset of the patients enrolled in the following cohorts an additional mandatory blood samples was taken for additional PK analysis (see section 13.3 Pharmacokinetic measurements – collection completed in meantime

Plasma PK [2] for subset of 24 pts.	cycle 1							cycle 2							cycle 3	
	day 14							day 1	day 14						day 1	day 14
	pre-dose	1h post-dose	2h post-dose	4h post-dose	6h post-dose	8h post-dose	24h post-dose	pre-dose	pre-dose	2h post-dose	4h post-dose	6h post-dose	8h post-dose	24h post-dose	pre-dose	pre-dose
placebo/ palbociclib + tamoxifen									x	x	x	x	x	x		
placebo/ palbociclib + anastratozol	x	x	x	x	x	x	x									
placebo/ palbociclib + gosereline + tamoxifen								x	x						x	x

4. TABLE OF CONTENTS

5. LIST OF ABBREVIATIONS

ABC	Advanced Breast Cancer
ASCO	American Society of Clinical Oncology
AE	Adverse Event
AESi	Adverse Event of special Interest
ALT	Alanine Aminotransferases
AI	Aromatase Inhibitor
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferases
AUC	Area Under the Curve

BC	Breast Cancer
CAP	Chest, Abdomen, Pelvis OR College of American Pathologists depending on context.
CCND1	Cyclin D1
CDK	Cyclin-Dependent Kinase
CDKN2A, $p16^{Ink4A}$	Cyclin-Dependent Kinase Inhibitor 2A
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridization
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
cCR	Clinical Complete Response
CR	Complete Response
CRF	Case Report Form
CSA	Clinical Study Agreement
CSF	Colony-Stimulating Factors
CT	Computed Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P-450
DC	Disease Control
DCR	Disease Control Rate
DFI	Disease Free Interval
DFS	Disease Free Survival
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

EDTA	Ethylenediaminetetraacetic acid
GnRH	A gonadotropin-releasing hormone analogue (GnRH analogue or analog), also known as a luteinizing hormone releasing hormone agonist (LHRH agonist) or LHRH analogue
eGFR:	Estimated Glomerular Filtration Rate
EIU	Exposure In Utero
EQ-5D	Dimension Health State EuroQoL Score
ER	Estrogen Receptor
FDA	US Food and Drug Administration
FDA	US Food and Drug Administration Administration Amendments
FFPE	Formalin Fixed Paraffin Embedded
FIH	First in Human
FISH	Fluorescent In Situ hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Hb	Hemoglobin
HDPE	High Density Polyethylene
HER	Human Epidermal Growth Factor Receptor
hERG	Human Ether-à-Go-Go Related Gene
HR	Hazard Ratio or Heart Rate depending on context
IB	Investigator's Brochure
IC_{50}	Concentration of 50% Inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IWRS	Interactive web response system
IEC	Independent Ethics Committee
IHC	Immunohistochemistry

INR	International Normalized Ratio
IORT	Intraoperative Radiation Therapy
IMPAKT	Improving Care and Knowledge through Translational Research
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ITT	Intent-to-treat
LFT	Liver Function Test
LHRH	A gonadotropin-releasing hormone analogue (GnRH analogue or analog), also known as a luteinizing hormone releasing hormone agonist (LHRH agonist) or LHRH analogue
LPD	Local Product Document
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NACT	Neoadjuvant chemotherapy
NCI CTCAE	National Cancer Institue Common Terminology Criteria
NCI	National Cancer Institute
NYHA	New York Heart Association
OBU	Oncology Business Unit
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PCD	Primary Outcome Completion Date
pCR	pathological Complete Response, pathological Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
pINV	pathological residual Invasive cancer

PK	Pharmacokinetic
PR	Partial Response or Progesterone Receptor (depending on context)
PR	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex.
PS	Performance Status
PRO	Patient Reported Outcome
PT	Prothrombin Time
QD	Quaque Die (once daily)
QRS	The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram. The QRS complex reflects the rapid depolarization of the right and left ventricles.
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QT_c	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's fomula
QTcF	QT interval corrected for heart rate using Fridericia's fomula
RANKL	Receptor Activator of Nuclear Factor Kappa B Ligand
RB/Rb	Retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RR	The interval between an R wave and the next R wave
R_{ac}	Accumulation Ratio
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SISH	Silver in Situ Hybridization
SD	Stable Disease or Standard Deviation (depending on context)
SPC	Summary of Product Characteristics
SmPC	Summary of Product Characteristics

$t_{½}$	Terminal Elimination Half-life
TdP	Torsade de Pointes
TEAE	treatment emergent adverse event
T_{max}	Time for C_{max}
ULN	Upper Limit of Normal
USPI	United States Package Insert
V_z/F	Apparent Volume of Distribution
WBC	White Blood Cell

6. INTRODUCTION

6.1 Neoadjuvant chemotherapy in breast cancer

The concept of moving systemic treatment from after surgery to before surgery was first developed based on a hypothesis that the earlier disseminated single tumor cells are being killed and the development of metastasis at a later stage is therefore less likely. However, trials conducted in the 80's and 90's of the last century have not confirmed this concept but found a similar outcome of patients treated with chemotherapy before or after surgery.[10] Thereafter neoadjuvant chemotherapy was mainly used to obtain a better operability of large operable or even inoperable locally advanced tumors. Today this approach is considered as a model to learn not only of the biology of breast cancer in general, but also of the treatment sensitivity of an individual patient's tumor. Tumor tissue obtained by core biopsy before treatment allows biological characterization of the tumor and development of an individual treatment plan. Early assessment after the first couple of cycles allows to test for functional predictors but also to change treatment according to early response. After completing all neoadjuvant treatment, histological examination of the surgically removed breast and axillary tissue allows precise assessment of tumor response and characterization of residual, treatment-resistant disease.

6.1.1 Pathological complete response is a prognostic marker for survival

It has been repeatedly shown that patients with a pathological complete response (pCR) after neoadjuvant chemotherapy have a better outcome than those without a pCR. However, the prognostic value varies for the different breast cancer subtypes.[11] [12] Especially in patients with HR-positive/HER2-normal tumors the association of a pCR with favorable outcome is only modest and in lower risk patients having highly or moderately differentiated tumors this association is even not existing. In fact, in this subgroup survival improvement was demonstrated without any increase in pCR rates.[13]

6.1.2 Extend of residual disease after neoadjuvant chemotherapy

Extent and characterization of residual disease after neoadjuvant chemotherapy raises increasingly more interest especially in patients with HR-positive/HER2-normal disease. The above mentioned meta-analysis[8] showed that the extent of residual disease after neoadjuvant chemotherapy in the breast as well in the nodes is associated with survival of patients. Worst prognosis with median survival of around 5 years was observed for patients with post-treatment persisting inflammatory breast cancer as well as significant (>10) involvement of axillary lymph nodes. Further characterization of residual disease included examination of Ki-67 on the residual tumor and, together with patients achieving pCR where Ki-67 was not detectable, analysis of a total of 1150 patients from the GeparTrio study for disease-free and overall survival.[14] Patients were subdivided into 4 groups (pCR, Ki-67 0-15%, Ki-67 15.1-35%, Ki-67 >35%) having significant different disease-free and overall survival. In fact, post-treatment Ki-67 measurements were prognostically more relevant than pre-

treatment measurements or changes from before to after treatment. When analyzing patients separately according to the hormone-receptor status of their tumor, it became obvious, that in hormone-receptor-positive disease, patients with low or moderate post-treatment Ki-67 levels had a comparable outcome to patients with a pCR and only patients with high Ki-67 levels showed a very high risk of relapse. In hormone-receptor-negative disease, however, patients with a pCR did better than those with low or moderate Ki-67 levels, and again, patients with highly proliferating tumors had a most unfavorable outcome.

However, as methodology and cut-offs of Ki-67 is not standardized, prognostic assessment by a clinical score post-neoadjuvant chemotherapy might be more appropriate as a risk selection tool in a global clinical trial. The clinical-pathologic stage – estrogen/grade (CPS-EG)[1,15]combining clinical stage before neoadjuvant treatment, pathological stage after neoadjuvant treatment, grading and estrogen-receptor status can be used to identify these high-risk patients. The score was further validated on 2454 patients with HR-positive/HER2-normal tumors from the German neoadjuvant studies' meta-database (F. Marmé, unpublished manuscript). In an updated version of this meta-database (n=2659) patients who have a score of 3 or higher or Score 2 and ypN+ disease show a 3-yrs DFS of 77% despite adjuvant endocrine treatment. The CPS-EG score allows identification of patients at increased risk of early relapse and allows to isolate a population of patients in whom testing of a new agent is indicated. This clinically driven selection approach allows further characterization of the tumors into subsets of molecularly different diseases using prospectively defined markers. This approach is thought to lead to determination of specific population of patients in whom use of palbociclib would be indicated.

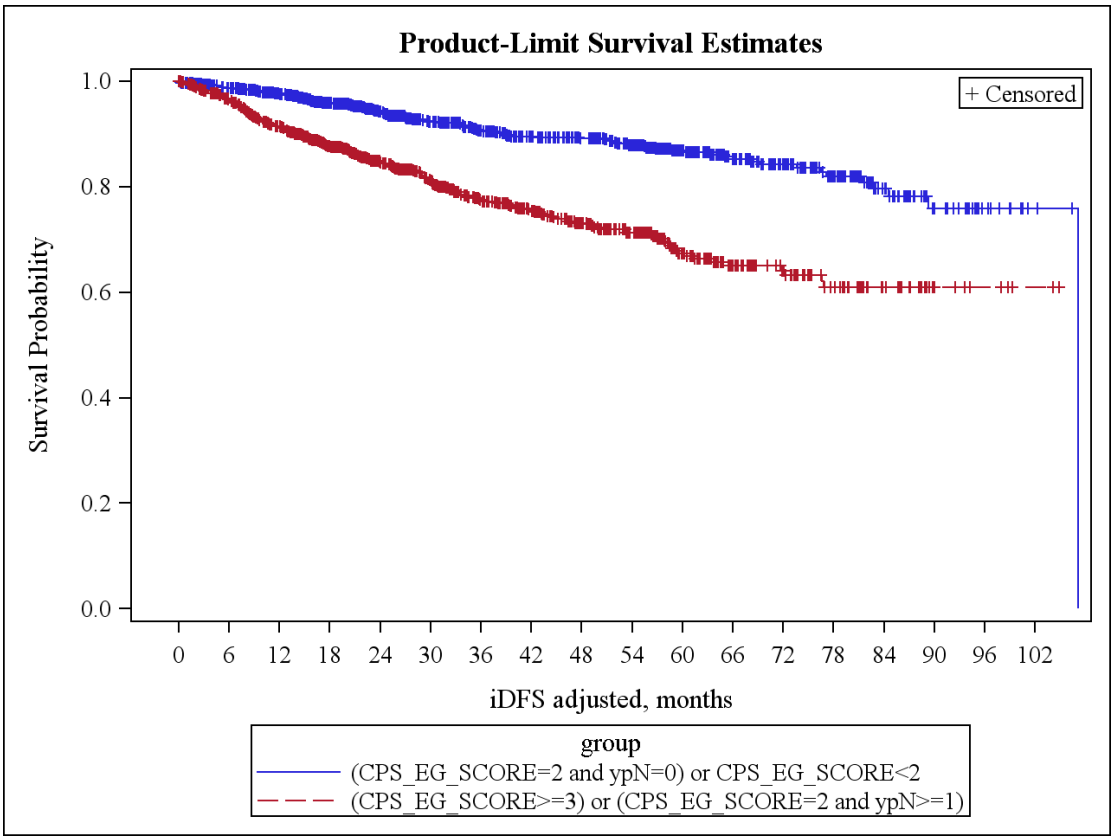


Figure 1: Survival after completion of radiotherapy (iDFS adjusted) in 2659 patients with HR-positive/HER2-normal tumors from the German neoadjuvant studies' meta-database by the CPS-EG score. The lower curve includes patients with 3 or more score points or score 2 and ypN+ status and the upper curve patients with less than 2 score points or score 2 and ypN-.

6.1.3 New concepts for post-neoadjuvant systemic treatment

Developing treatment strategies for those patients with unfavorable outcome due to residual disease after neoadjuvant chemotherapy appears a major task for the future. The NATAN study (NCT00512993) has recruited 693 patients with residual disease after anthracycline-taxane based chemotherapy and randomized them to 5 years treatment with zoledronic acid or observation. However, as 80% of the patients had hormone-receptor-positive disease and the patients were not otherwise selected for a high relapse-risk, event rate was much lower than expected. Results revealed no effect of zoledronic acid on survival with a median DFS of 73% overall.[16]. Due to the unfavorable outcome of patients without a pCR after neoadjuvant treatment with chemotherapy and trastuzumab, patients with HER2-positive tumors might be better candidates for such a post-neoadjuvant approach. A registration trial is currently under development with the aim to compare postsurgical treatment with trastuzumab to post-surgical treatment with trastuzumab emtansine (T-DM1), a fusion molecule of trastuzumab and an anti-microtubule agent derived from maytansine (Katherine study). So

far no post-neoadjuvant trial has been conducted for patients with high-risk HR-positive/HER2-normal tumors.

6.2 **The role of cyclin-dependent kinases in breast cancer**

6.2.1 Interaction of Estrogens and Cyclin-Dependent Kinases in Breast Cancer Cells

Studies of ER-positive breast cancer cell lines indicate that estrogens[17] and antiestrogens[18] act on sensitive populations of cells in early to mid-G1 phase. G1/S transition is under the control of CDKs activated by specific complex formation with regulatory cyclins. CDK4 and CDK6 are activated by binding to D-type cyclins and act early in G1 phase.[19 20 21 22]A primary target of CDK action in G1 phase is the retinoblastoma susceptibility gene product (Rb), which mediates G1 arrest through sequestration of transcriptional factors of the E2F-DP family. Phosphorylation of Rb and other members of the pocket protein family (p107 and p130) by active cyclin-CDK complexes leads to release of E2F and DP transcription factors and transcription of requisite genes for S-phase entry.[23]

D-type cyclins play an essential role in recognition of extracellular growth stimuli and initiation of G1 transit,[24 25] and several lines of evidence have linked estrogen regulation of cellular proliferation to cyclin D1 expression. Estrogen-induced proliferation of normal uterine and breast epithelium *in vivo* is associated with increased expression of cyclin D1 mRNA and protein.[26 27 28 29] Expression of cyclin D1 in breast tumor isolates correlates with ER-positive status.[30 31 32] MCF-7 breast cancer cells treated with estrogen exhibit increased expression of cyclin D1 mRNA and protein, formation of active cyclin D1-CDK4 complexes, and phosphorylation of Rb leading to G1 /S transition.[33 34 35 36] Estrogen-induced S-phase entry in these cells is inhibited by microinjection of antibodies to cyclin D1.[37] Anti-estrogen-induced growth arrest of ER-positive breast cancer cells is associated with decreased cyclin D1 expression.[38] Collectively, these studies are consistent with a model of estrogen action in which receptor activation induces increased cyclin D1 expression, CDK4 activation, and cell cycle progression. An upstream role for cyclin D1 has been suggested by recent reports describing direct physical interactions between cyclin D1 and the ER, leading to recruitment of steroid receptor co-activators and activation of ER-dependent transcription. This occurs in the absence of hormone and is independent of D-type cyclin association with CDK4.[39 40 41 42]

Constraint upon CDK activity and G1 progression is provided by the universal CDK inhibitors of the Cip-Kip family, including gp21Cip1 and p27Kip1, and the specific CDK4 and CDK6 inhibitors of the INK4 family, typified by $p16^{INK4a}$.[43 44 45 46 47] The CDKN2A gene product inhibits formation of active D-type cyclin-CDK complexes through specific binding interactions with CDK4 or CDK6 that prevent D-type cyclin-CDK association.[48 49 50]Over expression of $p16^{INK4a}$ in cells with functional Rb results in inhibition of both CDK4-and CDK6-associated kinase activity and Rb phosphorylation, with subsequent cell cycle arrest.[51 52] In addition, inhibition of D-type cyclin-CDK4 complex formation by $p16^{INK4a}$ prevents

sequestration of $p21^{Cip1}$ and $p27^{Kip1}$ by these complexes in early G1, leading to suppression of cyclin E-CDK2 activity. [53] [54] [55]

Overexpression of $p16^{INK4a}$ through adenoviral transduction of CDKN2A into MCF-7 cells leads to G1 arrest associated with inhibited CDK activity.[56] [57] Cell cycle progression induced by estradiol requires action of the steroid through mid-G1, well beyond the point of cyclin D1-CDK4 activation.[58] Functional association of cyclin D1-CDK4 is required for estrogen-induced CDK2 activation and G1/S transition and estrogen regulates expression of $p21^{Cip1}$, $p27^{Kip1}$, and Cdc25A independent of D-type cyclin-CDK4 function.[59]

6.2.2 Deregulation of Cell Cycle Related Genes and Proteins 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,[60] [61] [62] while the majority of human mammary carcinomas over express cyclin D1 protein.[63] [64] [65] Over expression of cyclin D1 is seen early in breast cancer, and it is maintained at all stages of breast cancer progression, including metastatic lesions.[66] [67] Amplification of the CDK4 gene, located at 12q13-q14, has been shown as an alternative genetic alteration to CDKN2A inactivation in various human tumor including breast cancer.[68] [69] There is a mounting body of evidence linking a specific CCND1 polymorphism (G/A870) to increased risk of cancer and outcome in a variety of tumor types including breast cancer. This polymorphism results in a splice variant, altered protein structure and enhanced oncogenic activity in experimental models.[70] The continued presence of CDK4-associated kinase activity is actually required to maintain breast tumorigenesis.[71] Direct analyses of primary tumors have revealed loss of Rb expression in 20–35% of tumors, and loss of heterozygosity or other alterations of the Rb locus in 7-37% of tumors.[72] [73] [74] [75]

In preclinical models, Rb depletion appears to be associated with resistance to antiestrogen therapy.[76] Finally, virtually all ER-positive cell lines harbor loss of $p16^{INK4a}$ [77] [78]expression, and low expression of CDK inhibitors p21 and p27 and high expression level of cyclin E and D1 have all been associated with resistance to anti-estrogen therapy.

6.3 **INVESTIGATIONAL PRODUCT**

6.3.1 Overview of palbociclib

Palbociclib (Molecular Weight free base: 447.53) is an orally active potent and highly selective reversible inhibitor of CDK4 and CDK6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase.

6.3.2 Preclinical Data

Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific Rb phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of Rb. The IC_{50} values for reduction of Rb phosphorylation at serine -780 and -795 in

MDA-MB-435 breast carcinoma cells were 0.066 and 0.063 µM, respectively. The IC_{50} values for reduction of Rb phosphorylation are similar to the IC_{50} values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

Palbociclib was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to palbociclib (IC50 < 150 nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell lines show the opposite characteristics. Sensitive cell lines in this panel represent mostly the luminal ER+ subtype.[79] The combination of palbociclib and aromatase inhibitors has been tested in preclinical models.[80] Additionally, the combination of palbociclib with tamoxifen has been tested in vitro in ER+ human breast cancer cell lines indicating a synergistic interaction[81]. This provides a biologic rationale for evaluating the combination of palbociclib with anti-hormonal therapy in the clinic.

Palbociclib has been evaluated in safety pharmacology, genetic toxicity, reproductive and development (fertility and early embryonic development, embryofetal development), and repeat-dose toxicity studies of up to 15-weeks duration in the rat and dog. Based on the nonclinical safety studies conducted with palbociclib, the primary palbociclib-related systemic toxicities were observed in hematolymphopoietic tissues (decreased cellularity, increased iron pigment, decreases in peripheral leukocytes and RBC parameters) and male reproductive organs (degeneration of seminiferous tubules, secondary epididymal hypospermia and increased intratubular cellular debris). Partial to complete reversibility of toxicities was demonstrated following a 4 week recovery period, with the exception of the male reproductive organ findings in the dog. These toxicities occurred in both rats and dogs, and are consistent with the intended pharmacologic effect of palbociclib (i.e., cell cycle inhibition) (Fink et al, 2001; Arguello et al, 1998; Bartkova et al, 2003). Palbociclib was also identified with the potential to cause QT prolongation (Section 6.3.4 Penelope Protocol), developmental effects, and aneugenicity. Developmental effects that were considered adverse included a decrease in fetal body weights in rats and a low incidence of small phalanges on the forepaws in rabbits. A no effect level for aneugenicity was observed at approximately 7-fold higher than unbound systemic AUC24 exposures associated with the human clinical dose of 125 mg QD.

Palbociclib is being further evaluated for chronic toxicity in a 6-month rat and 9-month dog repeat-dose toxicity study. (Administrative Letter1, Appendix 13, chapter 21.13) In Administrative Letter 1 we informed you, that Palbociclib is being further evaluated for chronic toxicity in a 6-month rat and 9-month dog repeat-dose toxicity study.

Following Data were released by Pfizer on 27th Jan 2014 as Special Safety Concern Report: The study entitled “27-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with PD-0332991 in Rats with a 12-Week Recovery Phase (Study 8282224; Sponsor Reference Number 13LJ036).

The identification of cataracts in rats following 27-weeks of intermittent dosing represented a potential new target organ toxicity. In the previous rat and dog repeat-dose toxicity studies up to 15 weeks duration, the primary target organ findings were observed in the hematolymphopoietic and male reproductive tissues.

The minimal dose level for cataract formation has not been identified from the 27-week rat toxicity study, based on the histological data (lens degeneration was noted microscopically). Cataracts were identified from ophthalmic evaluations at the lower examined dose of 30 mg/kg/day in males but at no dose in females.

While the impact of this nonclinical finding initially was considered to suggest a potential risk to human subjects, the overall benefit-risk for palbociclib remains favorable. (Administrative Letter 3, Appendix 21.15). Further data were communicated with Administrative Letter 5 (Appendix 21.17) that emerged from this toxicity study showing correlation between altered glucose metabolism and the formation of cataracts/lens degeneration. In dog toxicity studies (15-week and 39-week), no altered glucose levels or cataracts/lens degeneration have been observed (lack of lens degeneration not yet confirmed in the 39-week study; histopathology pending). Hyperglycemia and diabetes mellitus, are currently (July 2014) not considered to be identified clinical risks and are not considered to be adverse drug reactions (ADRs) of palbociclib. According to exclusion Criterion #10 a severe acute or chronic medical condition that may increase the risk associated with study participation needs to be excluded, which includes uncontrolled diabetes melittus. HbA1C levels need to be controlled while patient is under palbociclib treatment and in case of a signal the patients need to be refered to a diabetologist or a medical advisor to easily control the diabetes.

Once daily oral administration of palbociclib was well tolerated in rats at levels of 10 mg/kg/day for males and up to 200 mg/kg/day for females (Sponsor Reference No. 12LJ025)[82].

Addition of clinical information on glucose and cataracts from Study A5481023 in context of discussion of nonclinical data on glucose metabolism and findings of cataracts has been provided by the manufacturer via the update of the investigators brochue (Palbociclib IB, version December 2015). Given the lack of a signal of hyperglycemia or cataract development from the clinical experience and the fact that the finding of cataracts observed in young rats is most reasonably, based on now available aged rat toxicity studies, interpreted to be secondary to hyperglycemia, the manufacuters Risk Management Committee concluded that it was no longer warranted to include monitoring for hyperglycemia and ophthalmic changes in planned studies of the manufacturer. For the PenelopeB study, ophthalmic assessments have been removed as required study assessment by the sponsor.

6.3.3 Human Pharmacokinetic (PK) Data

As of 31 August 2016, twenty-seven clinical studies have evaluated the PK of palbociclib. Eight of these trials were conducted in patients with advanced malignant disease. Nineteen Phase 1 clinical pharmacology and biopharmaceutic studies of palbociclib were conducted in healthy subjects. Eleven of these 19 clinical trials were clinical pharmacology studies conducted to investigate the absorption, distribution, metabolism, and excretion of palbociclib as well as examine the potential for DDI with palbociclib. The remaining 8 of the 19 clinical trials were biopharmaceutic studies conducted to examine the bioavailability, bioequivalence, and food effect of the palbociclib formulations.

Pharmacokinetic parameters are available from all 74 patients enrolled in Study A5481001 (a first-in-human dose-escalation study in patients with advanced cancer) following multiple-dose administration (Day 8 of Cycle 1) at daily doses ranging from 25 to 225 mg of palbociclib. In addition, PK parameters are also available for nine patients on Day 14 of Cycle 1 (from patients on Schedule 2/1, i.e., 2 weeks on treatment followed by 1 week off treatment) and 4 patients on Day 21 of Cycle 1 (from patients on Schedule 3/1, i.e., 3 weeks on treatment followed by 1 week off treatment). The exposure (AUC(0-10) and C_{max}) increased in a dose proportional manner (i.e. dose linearity) over the dose range of 25 to 225 mg QD following palbociclib administration on Days 1 and 8 of Cycle 1, although some variability (low to moderate) around these doses was observed particularly at the 150 mg QD dose level. Following repeated daily dosing to Day 14 and Day 21 palbociclib was absorbed with a median T_{max} of ~4 hours when fasting 2 hours before and after palbociclib administration. The mean palbociclib Vz/F was 3103 L, which is significantly greater than total body water (42 L), indicating that palbociclib extensively penetrates into peripheral tissues. The ability for palbociclib to cross the blood brain barrier in humans is unknown. In rats, palbociclib displayed minimal ability to cross the intact blood brain barrier. Palbociclib was eliminated slowly; the mean $t_{½}$ was 26.5 hours (ranged 15.8 to 36.2 hours) and the mean CL/F was 86.1 L/hour. Palbociclib accumulated following repeated dosing with a median R_{ac} of 2.4, which is consistent with a half-life of ~27 hours.

Pharmacokinetic data from Study A5481002 indicate that palbociclib exposure at steady state in mantle cell lymphoma patients is similar to that observed in solid tumors (Protocol A5481001).

Pharmacokinetic analysis of the Phase 1 portion of Study A5481003 (Paloma-1/Trio-18, breast cancer, combination with letrozole) was conducted to evaluate the potential for drug-drug interaction between palbociclib and letrozole. The results indicate lack of a potential for drug-drug interaction between palbociclib and letrozole when administered in combination. See section 6.3.6 for further details.

The effect of food on the bioavailability of palbociclib when administered as the commercial free base capsule (the formulation being used in the PENELOPE Study), was investigated in Study A5481021. The administration of the free base formulation of palbociclib with food (including a high fat or a low fat meal given together with palbociclib, or moderate fat meals given 1 hour before and 2 hours after palbociclib) resulted in more uniform drug absorption and significantly reduced the intersubject variability in drug exposure when compared to the administration of the commercial free base formulation of palbociclib in a fasted state. Because of these findings, patients should be instructed to take palbociclib/placebo with food. This may begin immediately. This change does not significantly affect the study's scope, safety, or scientific quality. (Administrative Letter 2, Appendix 14, chapter 21.14). Comparison of the palbociclib isethionate capsule formulation given under both the overnight and minimal fasting conditions and the palbociclib commercial free base capsule formulation with food was found to be bioequivalent (Study A5481036).

The solubility of the palbociclib free base is pH dependent—palbociclib is water soluble at low pH (2.1-4.5), while the solubility dramatically decreases as pH rises above 4.5. Concomitant administration of agents which increase gastric pH can alter the solubility and absorption of palbociclib free base formulations.

Study A5481038 evaluated the effects of staggered dosing of the H2-receptor antagonist (H2RA) famotidine, and of the staggered dosing of the local antacid Mi-Acid Maximum Strength Liquid on the PK of a single oral 125 mg palbociclib free base capsule given with food in healthy subjects. The results indicated that administration of palbociclib under fed conditions with staggered famotidine and staggered Mi-Acid Maximum Strength Liquid dosing had no impact on the exposure of palbociclib.

Study A5481038 also evaluated the effects the coadministration of a single 125 mg dose of the free base capsule of palbociclib following multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions in healthy volunteers. Concurrent administration of rabeprazole with palbociclib decreased palbociclib Cmax by 41%, but had limited impact on AUCinf (13% decrease) compared with a single dose of palbociclib administered alone. This 13% reduction in overall exposure is not thought to be clinically relevant.

Given the reduced effect on gastric pH of H2RAs and local antacids compared to PPIs, the effect of dosing these classes of acid-reducing agents palbociclib exposure when given simultaneously with palbociclib free base capsules under fed conditions is expected to be minimal [83 84] .

In another DDI study (Study A5481018) in healthy subjects, the coadministration of a single 125 mg dose of the free base capsule of palbociclib with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUCinf and Cmax by 62% and 80%, respectively, when compared with a single dose of palbociclib administered alone. This study readout during the conduct of the PENELOPE study, resulting in an administrative letter prohibiting the use of PPIs and recommending the use of alternative treatments (such as

H2RAs or local antacids given by staggered dosing) when required (Administrative Letter 3, Appendix 15, chapter 21.15). This study also prompted the design and conduct of another clinical study evaluating the effects of gastric acid-reducing agents on palbociclib PK when palbociclib free base capsules were administered in the fed state (Study A5481038, discussed in the preceding paragraphs).

Collectively, these antacid DDI data further support the requirement that the free base capsule of palbociclib should be taken with food. Thus, to decrease inter- and intra-subject variability in palbociclib drug exposure as well as to minimize the DDI potential of concurrent administration of gastric acid-reducing agents, the palbociclib free base capsule formulation should be taken with food.

Update to Administrative Letter 3, Appendix 15, chapter 21.15: The results from the recently performed study A5481038, "A Phase 1, Open-Label Fixed-Sequence 2-Period Crossover Study Of Palbociclib In Healthy Subjects To Investigate The Potential Effect Of Antacid Treatment On The Pharmacokinetics Of A Single Oral Dose Administered Under Fasted Conditions" suggest that coadministration of a single 125 mg dose of pablociliclib with multiple doses of the proton pump inhibitors (PPI) rabeprazole under fed conditions decreased palbociclib Cmax by 41%, but had limited impact on AUCinf (13% decrease), when compared to a single dose of Palbociclib administered alone. Given the reduced effect on gastric pH of H2 receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid-reducing agents on palbociclib exposure under fed conditions is expected to be minimal. Under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists, or local antacids on palbociclib exposure.

As a result of these findings, the use of proton pump inhibitors is no longer refrained.

Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. An exploratory evaluation of the circulating metabolites for palbociclib was conducted in plasma samples obtained from patients treated with palbociclib 200 mg QD (Schedule 2/1) in Study A5481001. Assessment of the pooled plasma samples on Day 14 of Cycle 1 indicated that the glucuronide conjugate of palbociclib and the lactam of palbociclib (PF-05089326) were the main metabolites present in plasma. Glucuronide conjugate of palbociclib is unlikely to be active vs the intended target (CDK4/6). Although PF-05089326 showed similar in vitro activity vs CDK4/6 as with palbociclib, the unbound exposure of this metabolite is considerably lower than the parent drug. Therefore, contribution of this metabolite to the pharmacologic activity in humans is anticipated to be low. Other metabolites observed were the glucuronide conjugates of hydroxylated palbociclib and the glucuronide conjugate of reduced palbociclib. PF-05089326 was also observed in the circulation of rats following repeated daily oral administration of palbociclib. Plasma protein binding of palbociclib and PF-05089326 is ~85% and 95%, respectively.

The effect of multiple dosing of palbociclib (125 mg QD) on the single-dose PK of a sensitive CYP3A4/5 probe substrate, midazolam (2 mg), was evaluated in 26 healthy fasted women of nonchildbearing potential in Study A5481012. Coadministration of palbociclib and midazolam increased midazolam AUCinf and Cmax by 61% and 37%, respectively, relative to midazolam given alone. The ratios (90% CIs) of the adjusted geometric means for midazolam AUCinf and Cmax were 161% (146% 177%) and 137% (124% 152%), respectively, following administration of midazolam with multiple doses of palbociclib (Test), relative to midazolam administered alone (Reference). These results indicate that palbociclib is a weak time-dependent inhibitor of CYP3A. Based on these results, physicians should be aware that the dose of sensitive CYP3A4 substrates with narrow therapeutic indices may need to be reduced when given concurrently with palbociclib.

The effect of multiple doses of itraconazole (200 mg QD), a strong CYP3A inhibitor, on the single dose PK of palbociclib (125 mg) was evaluated in 12 healthy fed subjects in Study A5481016. Coadministration of itraconazole and palbociclib increased palbociclib AUCinf and Cmax by approximately 87% and 34%, respectively, relative to those when palbociclib dose was given alone. The ratios (90% CIs) of the adjusted geometric means for palbociclib AUCinf and Cmax were 187% (173%-202%) and 134% (126%-143%), respectively, when palbociclib was administered with multiple doses of itraconazole (Test), relative to palbociclib administered alone (Reference). The concomitant use of strong CYP3A inhibitors including, but not limited to, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice should be avoided.

The effect of multiple dosing of a strong CYP3A4 inducer, rifampin (600 mg QD), on the single-dose PK of palbociclib (125 mg), was evaluated in 15 healthy fasted subjects in Study A5481017. Coadministration of rifampin and palbociclib decreased palbociclib AUCinf and Cmax by approximately 85% and 70%, respectively, relative to palbociclib given alone. The ratios (90% CIs) of the adjusted geometric means for palbociclib AUCinf and Cmax were 15.5% (12.0% 19.9%) and 30.2% (23.5% 38.7%), respectively, following administration of palbociclib with multiple doses of rifampin (Test), relative to palbociclib administered alone (Reference). The concomitant use of strong CYP3A inducers including, but not limited to, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort should be avoided.

The multiple dose PK of palbociclib in patients of the Asian race has been evaluated in Studies A5481008, A5481010, A5481019, and A5481023. While palbociclib geometric mean AUCinf and Cmax values were 30% and 35% higher, respectively, in Japanese healthy subjects compared with those in demographic-matched non-Asian healthy subjects, palbociclib steady-state AUC_{τ}, Cmax, and Ctrough values for Japanese and/or Asian (excluding Japanese)

patients with advanced breast cancer were comparable with those in non-Asian patients with advanced breast cancer in some study populations but were higher in others. Notwithstanding, the maximum tolerated dose (MTD) of palbociclib that was determined for Japanese advanced cancer patients for both palbociclib monotherapy and in combination with letrozole was identical to the MTD determined in the predominantly Caucasian advanced cancer patients. Likewise, the same dosing regimen had also been demonstrated to be tolerable in Chinese advanced breast cancer patients.

Based on analysis of the cumulative PK, safety, and efficacy data, no dose adjustment based on Asian race is necessary.

6.3.4 QTc Evaluation Data

A pharmacokinetic/pharmacodynamic analysis to evaluate the relationship between palbociclib exposure and ECG variables (RR interval and QTc) was developed using data from postmenopausal women with ER-positive, HER2 negative advanced breast cancer enrolled in the QTc analysis subgroup included in Study A5481008 that was conducted as the definitive QT interval prolongation evaluation for the palbociclib program. A total of 125 patients were enrolled in this subgroup to evaluate the effect of palbociclib on QT interval. Of these 125 patients, 77 were randomized to the palbociclib plus letrozole treatment arm and 48 were randomized to the placebo plus letrozole arm. A total of 2597 recorded individual QT intervals and 322 palbociclib concentrations obtained from 77 palbociclib plus letrozole-treated patients were included in the analysis dataset. The median (range) age and baseline body weight of patients in the analysis dataset was 62.0 (36-86) years and 72.3 (48.1-157) kg, respectively. Among the 77 patients, 70 patients provided a total of 320 matched PK-ECG pairs to evaluate the relationship between palbociclib exposure and ECG variables (RR interval and QTc). Following administration of a therapeutic regimen of 125mg palbociclib QD in combination with 2.5 mg letrozole QD, the observed plasma concentrations of palbociclib had a median (range) of 88.0 (14.7-210) ng/mL in the PK-ECG matched data. The average heart rate, RR interval, QT interval, QT interval corrected for heart rate according to Bazett (QTcB), QT interval corrected for heart rate according to Fridericia (QTcF), and QTcS (QT interval corrected for heart rate according to a studyspecific correction factor) at baseline for PK-ECG matched data were 76.0 beats per minute, 811 msec, 384 msec, 429 msec, 413 msec, and 415 msec, respectively. The results of the analysis indicated that palbociclib did not appear to have a concentration dependent effect on the heart rate. A slight positive linear relationship was observed between palbociclib concentrations and QTcS; however, at the mean or median steady-state palbociclib Cmax following administration of the recommended clinical dose of Palbociclib (125 mg QD) in patients with cancer, the predicted upper bound of the 1-sided 95% CI for the increase in QTcS was less than 10 msec. Palbociclib, when added to letrozole, did not prolong the QT interval to a clinically relevant extent at the recommended

dosing regimen according to the criteria described in the ICH guidance for Industry E14 (ICH E14). Similar results were obtained when QTcF and QTcB were used.

6.3.5 Palbociclib Dose Rationale

Palbociclib has been tested in a Phase 1 dose escalation Study (A5481001) in 74 patients with advanced cancer. Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on treatment/1 week off treatment) and Schedule 2/1 (2 weeks on treatment/1 week off treatment).

All DLTs observed in this study were related to myelosuppression and mainly consisted of Grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, neutropenia was reversible and non-cumulative. Other most common adverse events included fatigue, anemia, diarrhea, constipation, vomiting and dyspnea, all with mild to moderate severity. At the MTD, a greater proportion of patients on the 200 mg QD, 2/1 schedule had treatment-related TEAEs during and after Cycle 1 than patients on the 125 mg QD, 3/1 schedule although the proportion of patients with treatment-related neutropenia was similar with respect to the 2 dosing schedules, both during and after Cycle 1. One partial response was reported in a patient with testicular cancer. A total of 13/37 patients treated with Schedule 3/1 evaluable for efficacy experienced stable disease (SD), including 6 patients with SD lasting 40 weeks or longer. One of these patients was a woman with ER+ breast cancer who had previously received 7 lines of treatment for her disease. This patient remained on treatment for 80 weeks (7 cycles at 50 mg/d and 13 cycles at 75 mg/d) and eventually discontinued treatment due to disease progression. Based on the relatively improved safety profile of Schedule 3/1, and the efficacy results from this study, the Schedule 3/1 has been selected for further clinical development and the RP2D for this schedule was determined to be 125 mg/d. This schedule and associated RP2D was further explored in combination with letrozole in the Phase I/II study in patients with ABC described below.

6.3.6 Phase I/II Data in Combination with Letrozole in Advanced Breast Cancer

Based on the preclinical evidence that palbociclib is highly active in ER(+) cell lines and the encouraging safety and PK profiles observed in the initial clinical studies, a randomized, multicenter active-controlled Phase 1/2 Study (A5481003) was designed to assess the efficacy, safety and pharmacokinetics of letrozole 2.5 mg QD (continuously) in combination with palbociclib 125 mg QD (schedule 3/1) versus single agent letrozole 2.5 mg QD (continuously) for the first-line treatment of ER(+), HER2 (-) advanced breast cancer in postmenopausal women. Letrozole was selected as the active control based on its worldwide approval and use as standard of care for the first-line hormonal treatment of postmenopausal women with ER(+) advanced breast cancer.

Study A5481003 was comprised of a limited Phase 1 portion, aimed at confirming the safety and tolerability of the combination and excluding a PK interaction with the combination, and

a randomized Phase 2 portion aimed at evaluating the efficacy and safety of letrozole in combination with palbociclib when compared to letrozole alone in the first-line treatment of postmenopausal patients with ER(+), HER2(-) advanced breast cancer. The Phase 2 portion consisted of 2 parts. In Part 1, patient selection was based only on ER/HER2 status. In Part 2, patients were prospectively selected also taking into account tumor CCND1 amplification and/or p16 loss. In May 2012, 177 patients have been enrolled in this study and enrollment is closed. Twelve (12) were enrolled in the Phase 1 portion and 165 (66 and 99 in Part 1 and 2, respectively) were enrolled in the Phase 2 portion.

Results from the Phase 1 portion,[85] indicated no PK interaction between palbociclib and letrozole with mean AUC(0-24) of 2002 and 2043 ng•hr/mL (n=11) for palbociclib in the absence and presence of letrozole, respectively, and 1990 and 1730 ng•hr/mL (n=10) for letrozole in the absence and presence of palbociclib, respectively. The RP2D was determined to be 125 mg QD on Schedule 3/1 (3 weeks continuous treatment followed by 1 week off treatment) in combination with letrozole 2.5 mg QD continuously. Partial responses were reported for 3 (33%) out of 9 patients with measurable disease (3 had bone-only disease). Another 5 patients (42%) had stable disease for ≥ 6 months and the clinical benefit rate (PR + SD ≥ 6 months) was 67%. Eight (8) patients discontinued from the study due to disease progression, including 2 patients with clinical progression, 1 patient withdrew consent and 3 patients are still ongoing.

Two (2) interim analyses for the Phase 2 portion of the study have been conducted. The results of the interim analyses showed consistent trend of clinically meaningful improvements in progression-free survival (PFS; primary endpoint). In the first interim analysis (Part 1; N=66), the median PFS for the PD 0332991 plus letrozole arm was 18.2 months versus 5.7 months for the letrozole alone arm (HR=0.35; 95% CI: 0.17, 0.72; p=0.006). The second interim analysis (N=165) continued to demonstrate a statistically significant improvement in PFS (26.1 vs. 7.5 months, respectively; HR=0.37; 95% CI: 0.21, 0.63; p <0.001).

The combination of palbociclib plus letrozole was generally well tolerated with safety profile similar to palbociclib as a single agent. The most frequently reported treatment-related adverse events included neutropenia, leukopenia, anemia, and fatigue. There were febrile neutropenia reported to date in this study. Overall, 8 patients in the combination arm were discontinued from the study treatment due to an adverse event, of which 5 were considered treatment-related (grade 3 neutropenia [n=4] and ischemic colitis) and 1 patient from the letrozole alone arm.

These results indicate that the combination of palbociclib with letrozole is well tolerated with AEs similar to those seen with either palbociclib or letrozole when administered alone. Additionally, the combination demonstrated antitumor activity which was consistent with the sensitivity of ER(+) breast cancer observed in the preclinical models.

6.3.7 Combination with other endocrine agents

Palbociclib and Tamoxifen:

The potential for a DDI between palbociclib and tamoxifen is considered to be probable. Multiple enzymes are responsible for the metabolism of tamoxifen and its active metabolites including CYP3A4, CYP2C9, and CYP2D6. In vitro evidence suggest that tamoxifen and one of its primary active metabolites, 4-hydroxy-tamoxifen, are inducers of CYP3A4 enzymes. In clinical trials, co-administration of tamoxifen with letrozole and anastrozole (both CYP3A4 substrates) has resulted in decreased exposures (AUC) of each by 37% and 27%, respectively. Palbociclib is aCYP3A4 substrate and CYP3A4 is thought to be the primary route of the oxidative metabolim of pabociclib. Thus, the co-administration of tamoxifen and palbociclib may lead to lower circulating levels of palbociclib and require an upward dose adjustment in palbociclib if these two compounds are used in conjunction. Additionally, time-dependent inhibition of CYP3A4 has been observed in preclinical studies of palbociclib.

A fixed-sequence 2-period crossover drug-drug interaction (DDI) study to assess the effect of steady-state levels of tamoxifen and its active metabolites on the pharmacokinetics of single dose palbociclib in healthy volunteers was conducted to rule out a need for palbociclib dose-adjustments when used in conjuction with tamoxifen. The effect of multiple dosing of tamoxifen (60 mg QD for 4 days followed by 20 mg QD for 23 days), on the single-dose PK of palbociclib (125 mg), was evaluated in 25 healthy fasted subjects in Study A5481026. Administration of palbociclib in the presence of tamoxifen and its metabolites (4-hydroxy-tamoxifen, N desmethyl tamoxifen, and 4 hydroxy N desmethyl tamoxifen) at steady state showed that palbociclib exposure was comparable with that when palbociclib was given alone. The ratios (90% CIs) of the adjusted geometric means of palbociclib AUCinf and Cmax were 108% (104% 111%) and 116% (105% 129%), respectively, following administration of palbociclib with multiple doses of tamoxifen (Test) relative to palbociclib administered alone (Reference). These results indicate that it is not necessary to adjust palbociclib starting dose when coadministering with tamoxifen.

Prior to opening the PENELOPE^{B} Study, the pharmacokinetics of a single oral dose of midazolam, a sensitive CYP3A4 substrate, with and without palbociclib dosed to steady-state will be assessed in a healthy volunteer DDI study (A5481012). The results of this study have been communicated and are detailed in Section 6.3.3.

Palbociclib and anastrozole:

The potential for a clinically significant DDI between palbociclib and anastrozole is considered to be low. Anastrozole inhibited CYP1A2, 2C8, 2C9, and 3A4 in vitro with Ki values ~30-fold higher than the steady-state C_{max} values observed following a 1mg daily dose.

In vitro and in vivo assessments of oxidative metabolism have indicated the route of formation of the primary metabolite hydroxyanastrozole is predominantly through CYP3A4.

Time dependent inhibition of CYP3A4 has been observed in in vitro studies of palbociclib, thus palbociclib has the potential to inhibit the primary clearance pathway of anastrozole.

Palbociclib and Goserelin:

The potential for a clinically significant DDI between palbociclib and goserelin is considered to be very low. Goserelin is a synthetic decapeptide analogue of gonadotropin releasing hormone (GnRH) whose primary route of elimination is the cleavage of C-terminal amino acids followed by renal excretion. PK data from Study A5481023 was analyzed to evaluate the potential for DDIs between palbociclib and fulvestrant, as well as between palbociclib and goserelin, at steady-state. These data indicate a lack of any clinically relevant DDIs between palbociclib, fulvestrant, and goserelin when administered in combination.
The concurrent administration of goserelin did not have clinically relevant impact on the plasma PK of palbociclib in Study A5481023. Statistical comparisons of the palbociclib within-subject mean steady-state Ctrough in the presence and absence of goserelin, both ignoring (ANOVA) and accounting for (ANCOVA) demographic differences between the treatment groups, confirmed the lack of a clinically significant DDI. The adjusted geometric mean ratios ranged from 88.3% to 93.1%, which are not considered clinically relevant.
Likewise, the concurrent administration of palbociclib did not have a clinically relevant impact on the plasma PK of goserelin in Study A5481023. Statistical comparisons (ANOVA) of the goserelin within-subject mean steady-state Ctrough in the presence and absence of palbociclib confirmed the lack of a clinically significant DDI. The adjusted geometric mean ratio was 110%, which is not considered clinically relevant.
Therefore, there is no clinically relevant DDI between palbociclib and goserelin when the two drugs are coadministered. Further pharmacokinetic data will be collected from the initial cohorts of 24 participants of the PENELOPE^{B} study each receiving eitherpalbociclib and tamoxifen, palbociclib and anastrozole, or palbociclib and goserelin and tamoxifen (see Section 13.3 for details). These data will be used to explore the potential for DDIs between antihormonal agentsand palbociclib and the result will be used to inform dose adjustment if necessary at the PK stop.

6.3.8 Long Term toxicity data

In order to assess the potential for cumulative toxicity with long term administration of palbociclib, an analysis of commonly reported adverse events (neutropenia, leukopenia, fatigue, anemia, nausea, arthralgia, alopecia, diarrhea, hot flush) using time interval analysis (0-6m, 6-12m, 12-24, and >24m) was performed in Study A5481003 (N=83). This analysis did not show any evidence of cumulative or long-term toxicity with prolonged exposure, since there was an almost universal reduction in reporting frequency for these events as treatment duration increased. An additional analysis was done looking at the cumulative percentage of reports received following one year, two years, and following any duration of dosing. This analysis indicated that for virtually all adverse events examined (alopecia, anemia, arthralgia, asthenia, decreased appetite, diarrhea, dyspnea, epistaxis, fatigue, hot flush, leukopenia,

nausea, neuropathy peripheral, neutropenia, pyrexia, stomatitis, thrombocytopenia, URTI, and vomiting), the incremental increase of reported events following the initial year of exposure was marginal. Based on these analyses, there does not appear to be any evidence of cumulative toxicity. Long term administration of palbociclib for 2 years and beyond does not appears to be associated with an increased rate of adverse events.

7. RATIONALE OF THE STUDY

About one third of patients with hormone-receptor (HR)-positive, HER2-normal breast cancer and residual disease after neoadjuvant chemotherapy have a substantial risk of relapse. The clinical-pathologic stage – estrogen/grade (CPS-EG) combining clinical stage before neoadjuvant treatment, pathological stage after neoadjuvant treatment, grading and estrogen-receptor status can be used to identify these high-risk patients. The CPS-EG score was additionally validated in 2454 patients with HR-positive/HER2-normal tumors from the German neoadjuvant studies' meta-database. Patients who had a score of 3 or higher or Score 2 and ypN+ disease show a 3-years iDFS of 77% despite adequate local therapy and adjuvant endocrine treatment.

Cyclin dependent kinases (CDK), a group of serine/threonine kinases, play a key role in regulating cell cycle progression by interacting with specific cyclin proteins in luminal-type tumors.'

PD-0332991 (palbociclib) is an oral, highly selective inhibitor of CDK4/6 kinase activity that prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 to S phase through blocking retinoblastoma (Rb) phosphorylation. Preclinical studies identified luminal ER subtype, elevated expression of cyclin D1 and Rb protein, and reduced p16 expression as being associated with sensitivity to palbociclib.

Final results from a randomized phase II study (Paloma-1/TRIO-18) in 165 postmenopausal, ER+/HER2- metastatic breast cancer patients revealed a progression-free survival of 20.2 months when palbociclib was given in combination with letrozole compared to 10.2 months when letrozole was given alone (HR 0.49 (95% CI 0.32-0.75) ($p<0.001$). Patients preselected by CCND1 (the gene encoding for cyclin-D1) amplification and/or loss of p16 in the primary tumor did not show different results. Uncomplicated neutropenia (48% grade 3, 6% grade 4), anemia (4% grade 3, 1% grade 4), and fatigue (2% grade 3, 2% grade 4) were the most common grade 3 and 4 adverse events.

The PENELOPE^{B} study is designed to demonstrate that in the background of standard anti-hormonal therapy palbociclib provides superior invasive disease-free survival (iDFS) compared to placebo in pre- and postmenopausal women with HR-positive/HER2-normal early breast cancer at high risk of relapse after showing less than pathological complete response to neoadjuvant taxane- containing chemotherapy. Considering the high risk of recurrence in patients after neoadjuvant chemotherapy and a high CPS-EG score, palbociclib appears to be an attractive option with a favourable safety profile for these patients.

8. DISCUSSION OF THE STUDY DESIGN

8.1 Control Treatments

For patients with residual disease after neoadjuvant chemotherapy no specific alternative treatment is recommended except the use of 5-10 years of hormonal agents (tamoxifen, aromatase-inhibitors, LHRH agonists). As patients must have received an adequate cumulative dose and cycles of chemotherapy before surgery (except for those with tumor progression where broad resistance against chemotherapy has to be postulated), no additional post-operative chemotherapy is considered indicated. There are no new agents that are proven to help improve the outcome in this group of high risk patient. It therefore appears reasonable to use a placebo to palbociclib as control treatment.

8.2 Washout Periods and carry over Effects

Based on the available pharmacokinetic data showing a half-life of 27 hours, palbociclib should be completely washed out within a period of 7 days. Patients should therefore not have elective surgery or new cytotoxic treatment started within this time period after last intake of palbociclib.

8.3 Selection of Study Population

The study population was initially selected based on the biological subtype of breast cancer as available efficacy data for palbociclib is restricted to patients with HR-positive/HER2-normal metastatic breast cancer. For patients with this subtype pathological complete response after neoadjuvant chemotherapy per se does not provide clinically relevant prognostic information. Therefore, a clinical score based on tumor stage before and after neoadjuvant chemotherapy, estrogen-receptor status and grade (CPS-EG score) was chosen as an enrichment strategy to select patients at highest risk for relapse despite continued adjuvant endocrine therapy.[1,12] The score was developed and validated by the MD Anderson Hospital, Houston, USA, as a prognostic tool to calculate risk of relapse after neoadjuvant chemotherapy in all types of breast cancer, and was strongly correlated with prognosis in the hormone-receptor-positive subtype as well. However, validation of the score in 2454 patients with only HR-positive, HER2-normal disease from neoadjuvant studies of the German Breast Group/AGO-Breast group[86], confirmed the prognostic value in the subset of patients targeted in this trial. The CPS-EG score allows isolation of a population of patients at increased risk of early relapse and allows to isolate a population of patients in whom testing of a new agent is indicated. This clinically driven selection approach allows further characterization of the tumors into subsets of molecularly different diseases using prospectively defined markers. This approach is thought to help to potentially further determine the specific, biomarker defined population of patients in whom use of palbociclib would be indicated.

8.4 Rationale for Biomarker Assessment

Today neoadjuvant therapy is considered a model to learn not only about the biology of breast cancer and drug effect in general, but also about the treatment sensitivity of an individual patient's tumor. Tumor core biopsy before treatment allows biological characterization of the tumor and development of an individual treatment plan. After completion of neoadjuvant treatment, histological examination of the surgically removed breast and axillary tissue allows precise assessment of tumor response and characterization of residual, likely treatment-resistant disease. It also allows confirmation of the presence of initially diagnosed subset, as it is known that in rare cases a loss of hormone receptor or acquisition of HER2 can be found.[87,88]

The availability of both the initial diagnosis tissue and most importantly the residual tumor tissue for all patients at the time of entry to the PENELOPE^{B} trial provides an opportunity to confirm the diagnosis before randomization and compare the molecular profile with the tissue from original diagnosis. It also allows prospectively testing of important hypotheses regarding the use of the CDK4/6 inhibitor, palbociclib, in combination with anti-hormonal therapy in the adjuvant setting. It is believed that the large number of markers analyzed in the tissue before entry to the trial will render precious information regarding both anti-hormonal and palbociclib treatment sensitivity and resistance. The markers will allow for further sub-classification of the disease into luminal A and luminal B as well as RB-positive and RB-negative disease and define amplification and overexpression of genes and proteins relevant to the CDK4/6-related pathway. Further, access to tissue at the time of original diagnosis will allow a reference to a pre-chemotherapy status of the tumor.

Based on the data from the metastatic HR+ breast cancer, almost uniform presence of intact Rb in HR+ breast cancer and known CDK4/6 role in estrogen stimulated proliferation of breast cancer, it is hypothesized that all patients in PENELOPE^{B} will derive benefit from addition of palbociclib. Hence the primary endpoint is iDFS in the intent-to-treat (ITT) population. However, data set for assessment of markers of sensitivity is available in the metastatic breast cancer settings only. The data set is small to date and the preclinical studies evaluating the CDK4/6 related pathway are complex. Hence, a definitive prospective selection is not supported by available data and would be premature at this time. Therefore, certain specific secondary hypotheses, prospectively defined in statistical analysis plan, will be conducted to optimize understanding of possible patient subgroups benefit/risk effects based on measurable biological criteria.

As the population eligible for PENELOPE^{B} trial is heterogeneous with regard to molecular subtypes of HR+ cancer, these tests will further stratify patients with respect to both biomarkers related to RB pathway alteration and a pre-planned subgroup analysis of luminal B patients (based on a at the time of analysis (which will be around the final efficacy analysis) commercially available CE-marked tests (e.g. PAM50, EndoPredict® or any other newly available test) will be conducted.

The prospective hypotheses will be described in detail in the study statistical analysis plan. This approach is expected to lead to determination of specific subpopulation(s) in which palbociclib would demonstrate enhanced efficacy (eg, luminal B as assessed by PAM50), or a specific prognostic group or specific molecular alterations (eg, cyclin D1 overexpression or amplification or others) for whom the benefit/risk of palbociclib would be even greater. It is expected that this enhanced benefit/risk profile in a subpopulation of early breast cancer HR+/HER2 normal patients would be reflected in the indication and/or conveyed in the product labeling. It is understood that during the study conduct, new information might emerge related to important markers in the RB pathway, and these markers will be incorporated prospectively into the statistical analysis plan before unblinding or analyzing this study.

The prospectively defined hypotheses are important as the understanding of the CDK4/6 driven pathway in breast cancer is currently incomplete. Hence, palbociclib may lead to a significant improvement of iDFS with a moderate toxicity profile, but the treatment effect may be limited to, or predominantly seen in prospectively hypothesized subgroups, both at the time of diagnosis and at study entry. This assumption could support a recommendation that 1-year treatment with palbociclib in combination with endocrine therapy is indicated for patients with HR-positive/HER2-normal disease in the prespecified biomarker subgroups at high relapse risk.

Hypotheses to be tested in tumor samples from core biopsy at diagnosis and surgery:

- It is hypothesized that tumors with alterations in RB/CDK4/6 pathway are more s**ensitive to the combination of anti-hormonal therapy and palbociclib. The molecular alterations** are characterized by presence of pRB1 (or total RB1) alone or in combination with one of the following: e.g. overexpression or amplification of cyclinD1 (CCND1), CDK4, CDK6; absence of p16 or loss of CDKN2A

- It is also hypothesized that luminal B, higher risk population would achieve largest prolongation of iDFS; hence luminal B tumors or other high risk profile (defined by PAM50, Endopredict® or any other commercially available test at the time of analysis), at the time of diagnosis or after chemotherapy would be predictive of enhanced palbociclib benefit.

The rationale for the second hypothesis is briefly summarized here: Genetic aberrations leading to hyperactivation of cyclin D1-CDK4/6 are particularly common in ER+ breast cancer, consistent with its critical role in the tumorigenesis of this cancer subtype.[89, 90] CCND1 amplification and cyclin D1 overexpression correlates positively with ER+ status [91, 92, 93, 94] and is an independent poor prognostic factor in women with ER+ disease who received adjuvant tamoxifen therapy.[95] The recent report from The Cancer Genome Atlas (TCGA) project indicated that poorer prognosis ER+ disease (luminal B) is preferentially enriched with gene amplification of cyclin D1 (luminal A: 29%, luminal B: 58%), and CDK4 gain (luminal A 14%, luminal B 25%).[96] Importantly RB1 (Rb), which is required for the activity of CDK4/6

inhibitors, is wild type in most luminal/ER+ breast cancers (unlike ER- disease), making CDK4/6 inhibitors particularly attractive agents for ER+ breast cancer.

The TCGA breast cancer study also showed low levels of RB1 mutations in luminal-type breast cancer (~1%) and frequent amplification of cyclin D1 (40%).[97]

The cyclin D1/CDK4/6 complex phosphorylates the retinoblastoma (Rb) protein, which leads to cell-cycle activation.[98] Results from several studies indicate that CDK4 and CDK6 play an important role in estrogen-stimulated proliferation of breast cancer cells in early to mid G1 phase. [99] [100] [101] [102] [103] Thus, CDK4 and CDK6 represent valuable therapeutic targets of ER+ advanced breast cancer[104]. Consistent with this conclusion, high levels of expression of the Rb-regulated E2F gene family is a frequent feature of endocrine-resistant luminal-type breast cancer. Unlike basal-like breast cancers, in which Rb loss is common[105], inhibition of the critical cell-cycle inhibitory effect of Rb in luminal tumors is achieved primarily through overexpression or amplification of cyclin D1, overexpression or amplification of CDK4, and/or loss of the CDK inhibitors CDKN1B, CDKN2A, and 2B. [106],45 Luminal tumors are therefore likely to prove sensitive to CDK4/6 inhibitors as randomized Phase 2 trials are under way (NCT00721409), [107]and a preliminary report of a randomized trial of letrozole versus letrozole plus palbociclib at the 2012 IMPAKT meeting in Brussels and San Antonio Breast Cancer meeting in December 2012 [108]showed significant improvement in progression-free survival.[109] Interestingly, mantle cell lymphoma, another chemotherapy-refractory cyclin D–driven malignancy, is also sensitive to CDK4/6 inhibition. [110]Basal-like tumors, and occasional luminal B tumors, harbor loss or mutation in Rb and are therefore highly unlikely to be responsive to these agents; thus, determination of the mode of Rb pathway inactivation will be critical to the success of CDK 4/6 inhibitors in breast cancer.[111]

8.5 Removal of Patients from Therapy or Assessment

Patients with progressive disease, medical or subjective intolerability of toxicity, or lack of compliance will be removed from the treatment with palbociclib or placebo. However, the investigators are asked to continue medical treatment as closely as possible to the guidelines given by the protocol. These patients will be followed up for relapse and toxicity as long as the patient does not withdraw her consent.

8.6 Blinding

The allocation of patients to either palbociclib or placebo will be blinded to patients and investigators. Neither the Investigator nor the Sponsor will have access to the individual data for the primary efficacy parameter obtained after the baseline visit in each patient. However, the Independent Data Monitoring Committee (IDMC) will review the blinded data for the safety and primary efficacy parameter in overall descriptive statistics during data review meetings. The descriptive statistics for use in any data review meeting will be generated by the GBG statistician/programmer. Only at the reasonable request of the IDMC, unblinded safety and/or efficacy results will be presented. The analysis will be conducted by an

independent GBG statistician, who is not involved in the study operation and execution. The DDI assessment will be conducted by Pfizer and supplied to the IDMC. The procedure for unblinding data to use for analysis of DDI assessment by the core laboratory will be described in the PK unblinding plan.

8.7 Rationale for the duration of treatment

Duration of treatment was determined by the time considered acceptable for patients having received neoadjuvant chemotherapy based on the available safety profile and experience with palbociclib. As the annual risk of relapse appeared to be stable over at least 5 years, an optimal duration of treatment could not be identified based on the relapse profile and a year of treatment was chosen arbitrarily.

8.8 Treatment Compliance

Compliance is monitored by a patients' diary recording date and time of capsules intake as well by counting the number of capsules brought back by the patient before starting the next cycle. This information will be documented in a summarized form in the electronic data capturing system (e-CRF).

No laboratory tests for compliance will be used.

8.9 Appropriateness of the Primary Efficacy Variable

The primary endpoint of this protocol, iDFS, is defined according to a recent position / paper of Hudis C et al.[112] In this paper it is stated that: "Overall survival has been recognized as the least ambiguous and most clinically relevant clinical end point in clinical trials of cancer therapy. However, in evaluating postoperative treatment for stage I, II, and IIIA breast cancer where all identifiable tumor has been resected, disease-free survival is frequently employed as a surrogate."

Nevertheless, follow up of patients will continue for further 3 years after the required events for the final iDFS analysis has been observed as this will allow to adequately determining the effect of palbociclib on overall survival. As the final efficacy analysis will be conducted after the last patient stopped treatment with palbociclib, cross-over is not expected to occur. However, during the conduct of the study, palbociclib has received market approval for the treatment of metastatic breast cancer in some countries, therefore some patients in the control arm as well as in the palbociclib arm) might be (re-)treated with palbociclib after relapse.

8.10 Risk-benefit Analysis for the Participants

All study participants must have received a standard taxane-containing neoadjuvant chemotherapy using regimes comparable to those currently used as adjuvant treatment, adequate surgery, as well as radiotherapy, if indicated. All patients will also receive adjuvant

endocrine treatment according to institutional standards. It is not expected that toxicity of palbociclib will reduce compliance with endocrine treatment. As currently no other kind of treatment is recommended for this subtype of breast cancer, under-treatment of study participants can be excluded.

Data of a large randomized phase II metastatic breast cancer trial (A5481003) showed a prolongation of median progression-free survival by palbociclib of 10.0 months corresponding to a hazard risk ratio of 0.49. Median progression free survival increased from 10.2 months for patient treated with letrozole alone to 20.2 months for patients treated with the combination of letrozole, The toxicity profile of palbociclib at the dose and schedule similar to the one that will be used in the PENELOPE^{B} study, was moderate with neutropenia being the most frequent treatment related adverse event. The clinical picture of neutropenia seen with the palbociclib/letrozole combination in A5481003 is notable for being quickly reversible, noncumulative and uncomplicated and managed without the use of growth stimulating factors. In fact, the majority of patients have discontinued from this randomized 165 patient study due to disease progression rather than from adverse events. While the neutropenia seen in the A5481003 advanced breast cancer setting has been managed using dose modifications, this has resulted in a high rate of dose interruptions (70%). In the early breast cancer setting to help mitigate this on target toxicity, a more aggressive dose reduction algorithm will be employed.

Data on cumulative toxicities seen with 1 year of palbociclib treatment as well as late toxicities after treatment discontinuation is available on >300 patients, and further data is being collected in a large clinical trial program in parallel to this study.

As described before, there are no obvious differences in the clinical and laboratory safety profile between patients taking palbociclib for less than 12 months compared to those taking the compound for 12 months or longer based on data collected in clinical studies to date. It is concluded that the data available do not identify any safety concerns associated with long term administration of palbociclib.

In addition, participating patients in the current trial will have marginal additional burden due to investigations required for study participation (e.g. additional visits at the site, additional blood tests, additional ECGs, and completion of questionnaires). However, the option to receive a treatment potentially significantly improving iDFS in this high-risk population is considered to balance uncertainties of the toxicity profile of palbociclib and the additional burden related to study investigations.

8.11 **Interpretation of Potential Study Results**

Four scenarios of results can be envisaged which will lead to the following conclusions:

- Palbociclib will lead to a significant improvement of iDFS with a moderate toxicity profile allowing the majority of patients to receive treatment at planned dose and schedule. This will support a recommendation that one year treatment with

palbociclib in combination with endocrine therapy is indicated for patients with HR-positive/HER2-normal disease at high relapse risk.

- Palbociclib will lead to a significant improvement of iDFS, but compliance with treatment is significantly impaired by toxicities. This might support a recommendation that one year treatment with palbociclib should be considered for selected group of patients with HR-positive/HER2-normal disease (e.g. at very high relapse risk, or based on predictive markers investigated in this study). Other doses and schedules will likely need to be explored.
- Palbociclib will lead to an overall significant improvement of iDFS with a moderate toxicity profile, but the treatment effect is limited to or predominantly seen only in prospectively hypothesized subgroups in which palbociclib is at planned dose and schedule. This will support a recommendation that one year treatment with palbociclib in combination with endocrine therapy is indicated for patients with HR-positive/HER2-normal disease in the relevant subgroups at high relapse risk.
- Palbociclib does not significantly improve iDFS in the study population. No recommendation will then be made to use this compound in this setting outside of clinical trials.

9. STUDY OBJECTIVES

9.1 Primary Objectives

To compare invasive disease free survival (iDFS) for palbociclib vs. placebo in patients with residual invasive breast cancer and high CPS-EG score - after neoadjuvant chemotherapy receiving standard adjuvant endocrine therapy for HR-positive/HER2-normal primary breast cancer.

9.2 Secondary Objectives

Secondary objectives:

To compare between the two arms:

- iDFS excluding second primary of non-breast cancers
- overall survival (OS)
- distant disease free survival (DDFS)
- locoregional recurrences-free (LRRFS) survival
- iDFS per treatment group in patients with luminal-B tumors (as determined by e.g. PAM50 or any other commercially available test at the time of analysis)
- compliance and safety according to NCI-CTCAE Version 4.0
- patients reported outcomes
- health economic outcomes

- to explore drug-drug interaction (DDI) potential for each palbociclib – endocrine combination therapy in a subset of this patient population
- to explore correlations between exposure and efficacy and/or safety findings;

Other objectives:

Scores and markers for their prognostic value in this specific trial setting and their predictive information on the efficacy and/or safety of palbociclib:

- pRB immunoreactive score in residual tumor after neoadjuvant treatment
- Cyclin D immunoreactive score in residual tumor after neoadjuvant treatment
- residual cancer burden (RCB)
- clinical response to neoadjuvant chemotherapy (assessed according to chapter 21.1)
- incidence and alterations in genes, proteins, and RNAs relevant to the cell cycle (eg, CCND1 amplification, CDKN2A deletion), drug targets (eg, CDK 4/6), and tumor sensitivity and/or resistance (Ki67, pRb, tRB, cyclin E, pi3k, p16, and other markers, measured by optimal test available at the time of analysis) in tumor tissues and/or peripheral blood.
- Low and high risk groups (defined by Endopredict®, ROR or other any other available test at the time of analysis)
- low and high risk groups defined by a standardized image analysis system for Ki67
- circulating tumor DNA (ctDNA)

10. STUDY DESIGN

This is a prospective, international, multicenter, randomized, double-blinded, placebo-controlled, parallel-group Phase III study comparing the efficacy and the safety of thirteen cycles (1 year) adjuvant treatment with palbociclib versus placebo in high risk (CPS-EG score 3-6 or CPS-EG score 2 and ypN+) patients without pathological complete response after neoadjuvant chemotherapy for hormone-receptor-positive / HER2-normal primary breast cancer. Patient will receive standard adjuvant endocrine treatment after completion of adequate local surgical and radiotherapeutic treatment. Prior endocrine treatment as part of neoadjuvant treatment is acceptable. Adjuvant endocrine treatment might have been started before randomization can be started anytime post-surgery.

The study has an adaptive design with two interim analyses including sample size re-estimation and non-binding stopping of the trial due to futility in the first and early stopping of the trial prematurely due to overwhelming efficacy in the second efficacy interim analysis.

Due to the adaptive design sample size will be at least 1100 patients. The sample size can be increased to a maximum of 1250 patients depending on the result of the first efficacy interim analysis.

Patients will be randomized in a 1:1 ratio to:

- Arm A: palbociclib at a dose of 125 mg once daily, day 1 to day 21 followed by 7 days off treatment in a 28-day cycle for thirteen cycles;
- Arm B: Placebo of palbociclib once daily day 1 to day 21 followed by 7 days off treatment in a 28-day cycle for thirteen cycles.

Randomization will be stratified using block randomization by:

- histological lymph node status at surgery (ypN 0-1 vs ypN2-3)
- age at first diagnosis (<=50 vs >50 yrs)
- centrally measured Ki-67 (>15% vs <=15%)
- global region of participating site (Asian vs non Asian)
- risk status (CPS-EG Score >=3 vs CPS-EG Score = 2 and ypN+)

Due to the prognostic impact of the randomization criterion risk status, randomization to the stratum CPS-EG score =2 and ypN+ will be limited to 50% of the patients.

Palbociclib/Placebo will be given for thirteen 28-day cycles or until diagnosis of invasive local, regional or distant recurrence, diagnosis of secondary malignancy, unacceptable toxicity, or withdrawal of consent of the patient or study termination by the Sponsor, whichever occurs first.

Patients in both arms shall receive standard endocrine treatment for at least 5 years.

11. STUDY POPULATION

11.1 Number of patients

Due to the adaptive design sample size will be at least 1100 patients. The sample size can be increased to a maximum of 1250 patients depending on the result of the first efficacy interim analysis.

11.2 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. Willingness and ability to provide archived formalin fixed paraffin embedded tissue block or a partial block from surgery after neoadjuvant chemotherapy and from core-biopsy before start of neoadjuvant chemotherapy, which will be used for centralized retrospective confirmation of hormone- and HER2-status and to evaluate correlation between genes, proteins, and mRNAs relevant to the endocrine and cell cycle pathways and sensitivity/resistance to the investigational agents. In case of bilateral breast cancer, tumor tissue of both sides needs to be assessable.

3. Histologically confirmed unilateral or bilateral primary invasive carcinoma of the breast.
4. Residual invasive disease post-neoadjuvant either in the breast or as residual nodal invasion.
5. Centrally confirmed hormone-receptor-positive (≥1% ER and/or PR positive stained cells) and HER2-normal (IHC score 0-1 or FISH negative (in-situ hybridization (ISH) ratio) <2.0 status) assessed preferably on tissue from post-neoadjuvant residual invasive disease or core biopsy of the breast, or if no other tissue is available the residual tumor of the lymphnode can be assessed.
6. Centrally assessed Ki-67, pRB, and Cyclin D1 status assessed preferably on post-neoadjuvant residual invasive disease of the breast, or if not possible, of residual nodal invasion or core biopsy. In case of bilateral breast cancer, tumor tissue of both sides needs to be assessable.
7. Patients must have received neoadjuvant chemotherapy of at least 16 weeks. This period must include 6 weeks of a a taxane -containing neoadjuvant therapy (Exception: Patients with progressive disease that occurred after at least 6 weeks of taxane-containing neoadjuvant treatment , a total treatment period of less than 16 weeks is also eligible).
8. Adequate surgical treatment including resection of all clinically evident disease and ipsilateral axillary lymphnode dissection. Histologically complete resection (R0) of the invasive and ductal in situ tumor is required in case of breast conserving surgery as the final treatment. No evidence of gross residual disease (R2) is required after total mastectomy (R1 resection is acceptable). Axillary dissection is not required in patients with a negative sentinel-node biopsy before (pN0, pN+(mic)) or after (ypN0, ypN+(mic) neoadjuvant chemotherapy.
9. Less than 16 weeks interval since the date of final surgery and date of randomization or less than 10 weeks from completing radiotherapy (whichever occurs last) at date of randomization.
10. Completion of adjuvant radiotherapy according to standard guidelines (e.g. AGO Mamma, NCCN) is strongly recommended. If radiotherapy is not performed the reason for this needs to be documented in the eCRF.
11. No clinical evidence for locoregional or distant relapse during or after preoperative chemotherapy. Local progression during chemotherapy is not an exclusion criterion.
12. A clinical-pathologic stage – estrogen/grade (CPS-EG) score of ≥3, or score 2 if nodal status at surgery is ypN+, calculated using local ER and grade assessed on either core biopsies taken before start of neoadjuvant treatment or surgical specimen (see chapter 21.1).
13. Age at diagnosis at least 18 years.
14. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (see 0).
15. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 4.0 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).

16. Estimated life expectancy of at least 5 years irrespective of the diagnosis of breast cancer.
17. 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.

11.3 **Exclusion Criteria**

1. Known severe hypersensitivity reactions to compounds similar to palbociclib or palbociclib/placebo excipients or to endocrine treatments.
2. Inadequate organ function prior to randomization including: Hemoglobin <10g/dL (100g/L) ANC < 2000/mm³ (< 2.0 x 10^9/L); Platelets <100,000/mm³ (< 100 x 10^9/L); AST or ALT >1.5 x upper limit of normal (ULN); alkaline phosphatase > 2.5 x ULN, total serum bilirubin > 1.25 x ULN; serum creatinine >1.25 x ULN or estimated creatinine clearance < 60 mL/min as calculated using the method standard for the institution; severe and relevant co-morbidity that would interact with the participation in the study
3. Evidence for infection including wound infections, Human Immunodeficiency Virus (HIV) or any type of Hepatitis
4. QTc >480.
5. Uncontrolled electrolyte disorders (eg, hypocalcemia, hypokalemia, hypomagnesemia).
6. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.0 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.
7. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.
8. Prior malignancy (including invasive or ductal in-situ breast cancer) within 5 years prior to randomization, except curatively treated basal cell carcinoma of the skin and carcinoma in situ of the cervix.
9. Current severe acute or uncontrolled chronic systemic disease (e.g. diabetes mellitus) 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.
10. Recent (within the past year) or active suicidal behavior.
11. Pregnancy or lactation period. Women of childbearing potential must implement adequate non-hormonal contraceptive measures (barrier methods, intrauterine contraceptive devices, sterilization) during study treatment and for 90 days after discontinuation. A serum pregnancy test must be negative in premenopausal women or women with amenorrhea of less than 12 months.
12. Major surgery within 2 weeks prior to randomization.

13. 10 weeks or more have passed since completion of radiotherapy at day of randomization and 16 weeks interval since the date of final surgery have passed.
14. Prior treatment with any CDK4/6 inhibitor.
15. Patients treated within the last 7 days prior to randomization and/or concurrent use of drugs known to be CYP3A4 inhibitors or inducers (see appendix 21.3).
16. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to randomization.
17. Male patients.

11.4 Removal of Patients from Study

11.4.1 Drop-outs without treatment

This study is conducted according to the principle of intent-to treat.

Drop-outs without treatment are defined as those patients who have been randomized in the study but withdrew their consent or are withdrawn by the investigator from the study immediately thereafter but prior to first application of study medication. The reasons are collected and reported in the Consort Statement. Such patients are to be included in the intent-to-treat analysis and will not be replaced.

11.4.2 Premature Treatment Discontinuation

Patients who have been randomized and have received study medication and, for whatever reason, did not participate throughout the entire study are classified as premature treatment discontinuation.

Patients may discontinue study treatment at any time. Reasons for discontinuation must be documented in the case report form (eCRF) and in the patient's medical records. Investigators must attempt to contact patients who fail to attend scheduled visits by telephone, letter, visit, etc., to exclude the possibility of an adverse event being the cause. Should this be the case, the adverse event must be documented, reported and followed-up as described in Section 17. A final examination should be performed if possible on each discontinuation. Patients should receive off study treatment as close as possible to the protocol. Treatment and outcome should be documented on the CRFs. In case a patient withdraws her consent for future data collection the CRFs have to be completed until the date of withdrawal.

12. STUDY TREATMENT

12.1 Method of assigning patients to treatment group

After a patient has completed the necessary screening visit procedures, the corresponding baseline CRFs have to be completed using the electronic data capturing MedCODES®

application. Central histologic assessment has to confirm an eligible tumor subtype (HR+/HER2-) as well to provide results of the biological stratification factors in a MEDCODES® interface. Eligibility of the patient will be checked and approved by GBG staff before randomization.

Patients will be randomly assigned to one of the two arms (palbociclib or Placebo) in a 1:1 ratio using a computerized system. Assignment will be stratified by the predetermined factors (see Section 10) using block randomization created by an independent GBG statistician not involved in the study conduct. Details of the computerized system procedure will be provided in the computerized system Site Manual. All data are collected and stored using the MedCODES® application.

Randomization should occur no more than 6 business days before administration of the first dose of investigational product. The site will receive confirmation of randomization and drug supply is ordered automatically via IWRS system.

12.2 **Breaking the Blind by Investigator**

12.2.1 During treatment with IMP

At the initiation of the trial, the trial site will be instructed on the method for breaking the blind. The method will be an electronic process in MedCODES®. Blinding codes should only be broken in emergency situations for reasons of patient's safety.. When the blinding code is broken, the date and reason for unblinding must be fully documented in source documents and entered on the case report form. However, every effort should be made by the site staff to ensure that the treatment arm in which the unblinded patient is assigned is not communicated to any sponsor personnel or designee involved in the conduct of the trial.

12.2.2 After IMP treatment discontinuation

Blinding codes may also be broken after a patient discontinues treatment due to disease relapse, as determined by the treating investigator using RECIST v.1.1 criteria or diagnosis of a second primary malignancy, but only if deemed essential to allow the investigator to select the patient's next treatment regimen and after discussion and agreement with GBG staff.

Code should not be broken in the absence of relapse of disease as per RECIST v.1.1 (e.g., in case of clinical deterioration, increase in tumor markers or any other evidence suggestive a relapse but in the absence of RECIST-defined new evidence of disease). In case of unblinding after treatment discontinuation, the "end of treatment" and "relapse form" have to be submitted via MedCODES® . The investigator can then send an unblinding request to the GBG unblinded statistician specifying the reason for unblinding. The unblinded information will then be shared as password protected file via email. Every effort should be made by the

site staff to ensure that the treatment arm in which the unblinded patient is assigned is not communicated to any sponsor personnel or designee involved in the conduct of the trial.

12.3 **Investigational Product**

12.3.1 Formulation and Packaging

- Palbociclib

Palbociclib will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. Capsules will be supplied in HDPE bottles containing 23 capsules. The capsules can be differentiated by their size and color (see below).

Table 1 Palbociclib/Placebo Capsule Characteristics

Dosage	Capsule color	Capsule size
75 mg	Sunset Yellow/Sunset Yellow	2
100 mg	Caramel/Sunset Yellow	1
125 mg	Caramel/Caramel	0

- Placebo of palbociclib

Placebo will be indistinguishable from the palbociclib capsules and will be supplied as capsules matching in size and color the various palbociclib formulations (see Table 1). Placebo capsules will be supplied in HDPE bottles containing 23 capsules.

12.3.2 Preparation and Dispensing

Palbociclib/Placebo will be provided in non-patient-specific bottles. The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Returned unused medication MUST NOT be re-dispensed to a patient.

Palbociclib/placebo is an agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Only one capsule strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously dispensed medication to the clinic and new capsules will be dispensed.

12.3.3 Administration

Palbociclib/placebo at a dose of 125 mg will be administered orally once a day at the same day time for 21 days followed by 7 days off treatment of every 28-day cycle, a delay of up to 3 days due to administrative reason is acceptable. A total of thirteen 28-day cycles should be administered palbociclib/placebo capsules will be administered together with endocrine treatment.). Patients should take Palbociclib /placebo with food.

Patients should be instructed to swallow palbociclib/Placebo capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day. Patients should be instructed to record daily administration of the study drugs in a patient diary.

Patients experiencing investigational product related toxicity may have their dose modified according to Section. 12.3.5.

General Rules:

- Patients who miss a day's dose entirely (latest intake 18:00 of a day) must be instructed NOT to "make it up" the next day.
- Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.
- Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose. Also refer to Section 12.3.10 for further details on medication errors and overdose.

12.3.4 Premedication and supportive treatment

No premedication or prophylactic supportive treatment is recommended.

12.3.5 Recommended Dose Modification

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of investigational product palbociclib/placebo may need to be adjusted as described in the following sections. Depending on the nature of the toxicity observed, dosing adjustment may be required for just one or both study drugs in the combination.

In the event of significant treatment-related toxicity, palbociclib/placebo dosing may be interrupted or delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

Dose modifications may occur in three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

12.3.6 Dosing Interruptions

Patients experiencing the following adverse events should have their treatment with palbociclib or palbociclib/placebo interrupted/delayed until criteria for retreatments are met (see 12.3.7):

- Uncomplicated Grade 3 or 4 neutropenia (ANC<1000/mm^3);
- Grade 3 or 4 neutropenia (ANC<1000/mm^3) associated with a documented infection or febrile neutropenia (fever ≥38.5°C with or without infection);
- Grade 3 or Grade 4 thrombocytopenia (Platelet count <50,000/mm^3);
- Non-hematologic toxicity persisting **despite optimal medical treatment** if either Grade 2 lasting more than 3 weeks or Grade ≥3 (excluding side effects likely related to endocrine treatment (e.g. joint pain of Grade 3) or alopecia ;
- Grade 3 QTc prolongation (QTc ≥501 msec on at least two separate ECGs).
- if a patient experiences concurrent > 3xULN ALT and 2xULN bilirubin the dose needs to be held while the cause is investigated.

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume are described in Section 12.3.7.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 12.3.8 unless expressly agreed otherwise following discussion between the investigator and GBG staff. If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

In the event of a treatment interruption **for reasons other than treatment related toxicity** (eg, non-cancer related surgery) lasting ≥3 weeks, treatment resumption will be decided in consultation with GBG medical staff.

12.3.7 Retreatment

Retreatment following treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- Platelet count ≥ 50,000/mm^3;
- ANC ≥ 1000/mm^3 and no fever; G-CSF is not generally recommended as secondary prophylaxis
- Grade 3 or higher treatment-related non-hematologic AEs considered related to palbociclib (including, nausea, vomiting, diarrhea, and hypertension **only** if persisting despite optimal medical treatment; not including alopecia) have recovered to Grade ≤ 1 or baseline (or, at the investigator's discretion, Grade ≤ 2 if not considered a safety risk for the patient).
- QTc ≤500msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTc remains above 480 msec, a cardiologist should be consulted and ECG should be monitored more frequently until QTc ≤480 msec.

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be adjusted as clinically indicated.

If the retreatment parameters are met within 3 weeks of treatment interruption or cycle delay, palbociclib/Placebo may be resumed. Please refer to Table 3 and 4 for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment) or 3 weeks of cycle delay, permanent discontinuation of palbociclib/Placebo treatment should be considered. Treatment resumption for patients recovering from treatment-related toxicity after >3 weeks of treatment interruption or cycle delay but deemed to be suitable to continue with a lower dose per the investigator's best medical judgment is recommended but left at the investigator's discretion.

12.3.8 Dose Reductions

Following dose interruption or cycle delay for palbociclib/placebo toxicity, a 2 step dose reduction schedule is recommended, when treatment is resumed.

No specific dose adjustments are recommended for Grade 1 or short lasting Grade 2 treatment related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

In case of a history of a grade 2 toxicity lasting for >3 weeks or grade 3 toxicity (both assessed in the presence of maximum supportive care, and as judged by investigator to be associated with palbociclib/placebo and to achieve easily manageable safety profile) a dose reduction is recommended in subsequent cycle (except for neutropenia, alopecia). For details please refer to Table 3 and 4. Dose reduction of palbociclib/placebo by 1 and, if needed, by 2 dose levels (Table 2) is recommended depending on the type and severity of toxicity encountered. In addition a break on day 10-12 or a prolonged holiday of up to 2 weeks after 2 weeks of treatment are further options to modify dose according to tolerability (if in investigator judgment such schedule is manageable and preferred). Taking palbociclib according to recommendation (with food) needs to be reinforced and checked. Alternatively patient will be discontinued from the study and entered into the follow-up phase of the study. All dose modifications/adjustments must be clearly documented in the patient's source notes and Investigational product administration CRF.

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that same reduced dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

Table 2 **Available Dose Levels**

Dose Level	**palbociclib/placebo for 3 out of 4 weeks (3/1 schedule)**
Starting dose	125 mg/d
-1	100 mg/d
-2	75 mg/d*
Discontinue Study Treatment or consider 75mg/d 2/2 schedule	

* **Palbociclib/placebo dose de-escalation below 75 mg/d is not allowed the schedule may move to 75mg/day two weeks on followed by two weeks**

Table 3: **Palbociclib/placebo Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment**.

Toxicity	**1st episode**	**2nd episode**	**Subsequent episodes**
Uncomplicated Grade 3 neutropenia *(ANC 500 to <1000/mm^3)* **with recovery to ≤ Grade 2 until planned D1 of next cycle**	Same dose level (DL)	Same DL	Same DL
Uncomplicated Grade 3 or 4 neutropenia without recovery to ≤ Grade 2 at planned D1 of next cycle **Uncomplicated grade 4 neutropenia (***ANC <500/mm3***) with recovery to** **≤ Grade 2 until planned D1 of next cycle**	Reduce to Dose Level-1 (DL-1)	DL-1 and break from day 10-12	DL-2 and break from day 10-12 Next episode stop ***or*** continue with 2 weeks treatment and 2 weeks holiday
Neutropenia grade 3 or 4 associated with a documented infection ; **Febrile neutropenia** **Thrombocytopenia grade 3 or 4**	DL -1 and either break from day 10-12 ***or*** 2 week drug holiday	DL -2 and either break from day 10-12 ***or*** 2 week drug holiday	Stop
Any grade 2 toxicities for more than 3 weeks (except for neutropenia or alopecia)	DL-1	DL-2	Stop

Non-hematologic toxicity grade 3 or 4 *(including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment; non-including alopecia)*	DL-1 Consider break from day 10-12 Consider DL-2 for 2 weeks ***or*** 2 weeks holiday if recovery is delayed	DL-2 Consider break from day 10-12 Consider DL-2 for 2 weeks ***or*** 2 weeks holiday if recovery is delayed	Stop
QT interval changes see table 4			

12.3.9 QTc prolongation management

In the event of QTc prolongation of **>480-500 msec**, possible alternative reversible causes such as serum electrolytes abnormalities, or usage of concomitant medications with the potential to prolong the QTc interval should be evaluated.

If such reversible causes are identified, then they should be corrected accordingly (ie, correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation (if possible) of concomitant medications known to prolong the QT interval).

Recommended dose modifications in the event of QTc prolongation are provided in Table 4.

Table 4 **Palbociclib/placebo Dose Modifications in the Event of QTc Prolongation**

	Toxicity (NCI CTC Grade, Version 4.0)		
	Grade 2 QTc prolongation QTc 481 - 500 ms	**Grade 3 QTc prolongation (>=501 msec)**	**Grade 4 QTc prolongation (>=501 msec or >60 ms change from baseline and life-threatening signs incl. Torsade de points)**
Reversible cause identified	Treat reversible cause Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec Continue at the **same dose level** (1)	Treat reversible cause Withhold treatment until QTc<500 msec Resume treatment at the **same dose level**. Monitor ECG more frequently as per investigator's best medical judgment until QTc≤480 msec.	Permanently discontinue
No reversible cause identified	Consult cardiologist and initiate more frequent ECG monitoring until QTc≤480 msec Continue at the **same dose level** (1)	Consult cardiologist. Withhold treatment until QTc<500 msec Resume treatment at the **next lower dose** level (2) Monitor ECG more frequently as until QTc≤480 msec.	Permanently discontinue

(1) If the QTc remains above 480 msec more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the study medical monitor, taking into account the emerging safety data from palbociclib trials and the investigator's best medical judgment.

(2) If the Grade 3 QTc prolongation occurs again after one dose reduction, further dose adjustment and/or discontinuation should be discussed with study medical monitor in consultation with a cardiologist, taking into consideration the emerging safety data from palbociclib trials and the investigator's best medical judgment.

12.3.10 Medication Errors and Overdose

Medication errors may result in this study from the administration or consumption of the wrong drug, by the wrong patient, or at the wrong dosage. Such medication errors are to be captured irrespective of the presence of an associated toxic event like an SAE on the SAE form. In the event of medication dosing error, GBG should be notified immediately.

12.3.11 Compliance

Patients will be required to return all bottles of palbociclib/placebo as well as the completed patient diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. The number of remaining capsules will be documented and recorded.

To be considered compliant, each study patient must have received at least 80% of the prescribed number of doses of palbociclib/placebo based on the number of days of actual dose administration. Dose adjustments must follow instructions provided in Section 12.3.4 - 12.3.8.

12.4 **Drug Storage and Drug Accountability**

Palbociclib/placebo capsules should be stored at controlled room temperature (15-30°C, 59-86°F) in their original container.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

To ensure adequate records, palbociclib/placebo capsules will be accounted for as instructed by GBG. Patients are requested to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

Storage conditions stated in this protocol or in the Investigator's Brochure (IB), United States Package Insert (USPI), Summary of Product Characteristics (SPC), or Local Product Document (LPD) may be superseded by the label storage.

Investigators and site staff are reminded to continuously monitor room storage temperatures and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for the room storage. Any temperature excursions must be reported immediately to GBG and documented. Once a deviation is identified, palbociclib/placebo MUST be quarantined and not used until GBG provides documentation of permission to use the investigational product.

At the end of the trial, GBG will provide instructions as to disposition of any unused investigational product. If GBG authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by GBG. Destruction must be adequately documented.

12.5 **Concomitant Medications**

Patients must be instructed not to take any additional medications (including over-the-counter (OTC) or other products) during the study without prior consultation with the investigator as some herbal supplements or OTC can impact pharmacokinetics of palbociclib/placebo and are in the list on prohibited medications. Any medications including herbal supplements, vitamins, or treatment taken by the patient from 28 days prior to the start of study treatment and up to 28 days following the last dose of investigational product and the reason for their administration must be recorded on the CRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anesthesia" on the concomitant treatment records; it is not necessary to list the specific anesthetics. Supportive care for cancer-related symptoms should be offered to all patients in this study.

12.5.1 Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

- **Anticancer agents:** No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than tamoxifen, LHRH analogues or aromatase inhibitors) will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted on study.
- **Strong CYP3A inhibitors/inducers:** palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans (see Section 6.3.3 for details). The concurrent use of CYP3A inhibitors, including amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and

grapefruit, grapefruit juice or any product containing grapefruit, are not allowed in the study. The concurrent use of CYP3A inducers, including carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort, are not allowed in the study (see also Appendix 21.3)

- **Hormone replacement therapy**, topical estrogens (including any intra-vaginal preparations), **megestrol acetate** and **selective estrogen-receptor modulators** (eg, raloxifene) are prohibited during the active treatment phase.

12.5.2 Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible**. If usage of the following treatments is deemed necessary, consultation and agreement with GBG is required prior to treatment initiation.**

- **Moderate CYP3A Inducers:** The concurrent use of moderate CYP3A inducers such as dexamethasone or modafinil is not recommended.
- **Sensitive CYP3A Substrates:**, As described in Section 6.3.3, palbociclib is a weak time-dependent inhibitor of CYP3A and caution should be exercised in patients receiving palbociclib in combination with drugs that are predominantly metabolized by CYP3A and have a narrow therapeutic window. In particular, co-administration of palbociclib with CYP3A4 sensitive substrates with narrow therapeutic index including, but not limited to alfentanil, aripiprazole, cyclosporine, ergotamine, fentanyl, halofantrine, pimozide, quinidine, sirolimus, tacrolimus, triazolam, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market) are not recommended during the active treatment phase of the trial. Alternative therapies should be used when available, but if use cannot be avoided the treating physician should be aware that dose reductions of the coadministered drug may be required.
- **Chronic immunosuppressive therapies** should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
- **Erythropoietin** for the supportive treatment of anemia.
- The use of **herbal medicine** is not recommended during the active treatment phase.

12.5.3 Permitted Medications

The following treatments are permitted throughout the duration of the active treatment phase:

- **Standard therapies** for pre-existing medical conditions, medical and/or surgical complications. Any medication intended solely for supportive care (eg, analgesics,

antidiarrheals, antidepressants) may also be used at the investigator's discretion. All medications should be recorded.

- **Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors**
  Patients may concurrently receive bisphosphonates or rank ligand inhibitors while on this study if necessary for treatment or prevention of osteopenia or osteoporosis.
  The need to initiate or increase the dose of these therapies during the study will not be considered as indicative of disease progression leading to the discontinuation of patient from the active treatment phase unless disease progression can be confirmed by adequate imaging methods.
- **Hematopoietic growth factors** (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]): Primary prophylactic use of granulocyte-colony stimulating factors is not permitted but they may be used to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guideline.[113] If neutropenic complications are observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered a reasonable alternative.

12.6 Concomitant Radiotherapy or Surgery

Any **concurrent radiotherapy is prohibited** throughout the duration of the active treatment phase of the study. Adjuvant radiotherapy should be completed before entering the study. Patients requiring radiotherapy during the active treatment phase will be discontinued from the active treatment phase and will enter the follow-up phase.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and palbociclib required to minimize the risk of impaired wound healing and bleeding, if any, has not been determined. Based on the available pharmacokinetic data, stopping palbociclib/placebo is recommended at least 7 days prior to elective surgery. Postoperatively, the decision to reinitiate palbociclib/placebo treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

12.7 Pregnancy and Lactation

Palbociclib/placebo as well as endocrine treatment must not be administered to pregnant women, or to women who are breastfeeding. Treatment has to be immediately been stopped as soon as a pregnancy is diagnosed.

A negative pregnancy test is required prior to study entry. Highly effective non-hormonal contraceptive methods that result in a low failure rate should be applied, i.e. some IUDs , sexual abstinence or vasectomised partner (CPMP/ICH/286/95). The use of hormonal contraceptives is not allowed during the entire duration of the study. Patients should be

advised not to get pregnant or breast feed during the first 3 months after the end of endocrine therapy.

In case a patient becomes pregnant during study treatment, endocrine therapy or 3 months thereafter, this has to be documented within one working day using the SAE reporting form and outcome of the pregnancy has to be reported on a separate form provided by GBG.

12.8 **Non-investigational Products**

12.8.1 Description, Formulation, and Handling of the non-investigational products

Current treatment guidelines recommend adjuvant endocrine treatment for 5 to 10 years after surgery for patients with hormone-receptor-positive disease. Adjuvant endocrine treatment might have already started before the patient enters the study.

Patients may be receiving either tamoxifen or aromatase inhibitor (AI: letrozole, anastrozole, or exemestane). For premenopausal patients, concurrent LHRH agonist use is allowable.

PK-DDI sampling was done for patients receiving Tamoxifen or Gosereline+Tamoxifen or Anastrozole as endocrine treatment.

Treatment should be performed according to institutional guidelines. Patients discontinuing endocrine treatment due to treatment-related toxicity should first be switched to another type of endocrine therapy. If again this treatment is not tolerated, the patient will be discontinued from the active treatment phase of the study and enter the follow-up phase.

Patients discontinuing palbociclib/placebo treatment due to treatment-related toxicity preferably continue endocrine treatment as per the investigator's discretion.

For all other information refer to the package insert (PI) and/or the summary of product characteristics (SmPC).

12.9 **Post-study Treatment**

After completion of palbociclib/placebo patients will continue with endocrine treatment for a total of 5 to 10 years. No other kind of treatment is recommended.

13. STUDY PROCEDURE - ASSESSMENTS AND SCHEDULE

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to

perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The monitor should be informed of these incidents in a timely fashion.

Safety assessment will consist of monitoring of all adverse events (AEs), including serious adverse events (SAEs), regular monitoring of hematology, serum chemistry, and routine monitoring of ECGs, physical examinations, vital signs, and ECOG performance status.

Adverse event assessment will include type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 4.0, see Severity Assessment section), timing, seriousness, and relatedness.

	Investigations prior to study entry to any protocol investigations or procedures - Prescreening	Timing (within days prior to randomization)
Imaging tests **	• **Breast ultrasound (<13 months) and either Bilateral mammography (< 13 months) OR bilateral breast MRI (<13 months). For women treated with mastectomy only imaging data of contralateral breast is required ; for women with bilateral mastectomy an imaging assessment as recommended per national guidelines should be available.** Other instrumental examinations only in case of symptoms suspicious for locoregional or distant relapse. Reports of these examinations < 13 month prior to enrollment must be available then. Bone scan, CT, MRI, and/or PET-CT scans may be performed as clinically indicated according to the investigator. Data including imaging from intial results for calculation of clinical score of CPS-EG needs to be available as source data.	• Imaging tests for staging < 13 Months
Surgery	**Surgery (breast-conserving surgery or ablation) excising the initial tumor bed. Subsequent secondary surgical interventions do not count regarding this time interval.** All surgery reports and all pre- and postneoadjuvant histopathology reports including information on the components of residual cancer burden (RCB) (primary tumor bed area, overall cancer cellularity (%), percentage of cancer that is in situ disease, number of positive nodes, diameter of largest metastases) have to be provided.	less than 16 weeks prior to randomization
Radiotherapy	**Completed adiotherapy after surgery according to guidelines** if indicated (IORT allowed). Radiotherapy reports including information of time period of radiotherapy, irradiated region and dose per region, dose per day have to be provided	less than 10 weeks prior to randomization

13.1 **Study Procedures at Screening**

	Investigations with Screening	Timing (within days prior to randomization)
Patient informed consent	• Obtained	Prior to any protocol investigations or procedures
History and physical exam	History - including: diagnosis of breast cancer, menopausal status, general medical history including cardiac history and allergy, concurrent illnesss, response to neoadjuvant chemotherapy (assessed according to Appendix1 21.1) • Concomitant medications, and their indication, used within one month prior to study entry • Physical exam - including: height and weight, ECOG for performance status according to Appendix 2, 21.2) / vital signs, heart rate (pulse), blood pressure • Palpation of breasts, axillae, supra- and infraclavicular region • Preexisting signs and symptoms • Check FSH and E2 in patients aged <55 and history of hysterectomy.	< 30 days
Hematology *	• Hemoglobin • White blood cells (WBC) and absolute neutrophil count (ANC) • Platelet count	< 8 days
Pregnancy Test	• Serum (if applicable) Highly effective non-hormonal contraceptive methods, (barrier methods, intrauterine contraceptive devices, sterilization) ; sexual abstinence or vasectomized partne	< 14 days (if applicable)

	Investigations with Screening	Timing (within days prior to randomization)
Biochemistry *	• Sodium, Potassium , total calcium, magnesium • Albumin • Alkaline phosphatase • ASAT (SGOT), ALAT (SGPT) • Total bilirubin • Serum creatinine	< 8 days
Biochemistry *	• HbA1C	< 30 days
Cardiac Monitoring	• 12-lead ECG including automated calculation of PR interval, QT interval, RR interval, and QRS complex	< 30 days
Biomaterials	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block from **post-neoadjuvant** surgically removed tissue or if not available, involved lymph nodes (mandatory). Formalin-fixed paraffin-embedded (FFPE) tumor tissue block from **pre-neoadjuvant** core biopsies for further exploratory analysis or to confirm luminal status (mandatory)	After ICF signature
	• 10 mL full blood for serum (mandatory) needs to be provided before 1st dosing with IP • 10 ml full blood for plasma (mandatory) needs to be provided before 1st dosing with IP	< 30 days but latest before 1st dosing with IP
	• 10 mL full blood for SNP analysis (mandatory) (can also be taken any time after randomization)	< 30 days but latest before EoT
	• 20 ml full blood for detection of ctDNA (optional)	< 30 days latest before 1st dosing with IP

	Investigations with Screening	Timing (within days prior to randomization)
Patient reported outcome / Health economics	• EORTC QLQ C30, • EORTC QLQ BR-23, • EORTC QLQ FA-13 Fatigue, • GAD7 patient self-rating mood scale • EQ-5D. See Appendix 5-8 (21.5 – 21.8) • Use of medical resources related to breast cancer and that may differ between trial arms****	< 14 days
Other Investigations	• as clinically indicated	< 30 days
* Laboratory assessments will be performed whenever possible by the same laboratory throughout the study. **Every effort will be made to use the same instrumental examination from baseline through follow-up. **** Medical resource use at the treating center should be recorded by study staff without involving the patient. Assessment of medical resource use by other health care providers and of lost resources (days of work etc.) should be based on patient interview		

13.2 **Evaluation during active treatment with palbociclib/placebo**

	Investigations during Treatment	Timing
History and physical exam** since previous visit	• Clinical history and concomitant medication • Physical exam – including: weight, ECOG performance status (Appendix 2, 21.2), heart rate , blood pressure • Adverse events* • Information on external hematology lab results or from site lab taken on day 1 of cycles 6,8,10,12 only	Days 1 (+/-2) and 14 during cycles 1 and 2, Day 1 (+3) at cycle 3, 4, 5, 7, 9, 11, 13 and at EOT. SAEs must be reported within 24 hours. For all randomized patients SAEs must be reported until 30 days after last intake of IMP once they received initial dose of study drug

	Investigations during Treatment	Timing
Hematology**	• Hemoglobin • White blood cells (WBC) and absolute neutrophil count (ANC) • Platelet count	Days 1 (+/-2) and 14 (+/-2) during cycles 1 and 2, Day 1 (+3) of 3, 4, 5, 6, 7,8, 9,10, 11, 12, 13 and at EOT, and clinically indicated.
Laboratory assessments will be performed whenever possible by the same laboratory ("site lab"). The exception are hematology labs on Day 1 of Cycles 6, 8, 10 and 12 which can be done at any laboratory conveniently located for the patient and if accepted per local EC/IRB with protocol approval. Results have to be sent immediately to the site for review. Abnormal external lab results (neutropenia <1000/mm³, thrombocytopenia <50.000/mm³ or anemia grade >=3) obtained on those dates and at a lab different from the site lab, must be repeated at the site lab within 2 days (=extra, but clinically indicated hematology lab), and the Investigator must immediately determine the impact on study drug dosing and further medical management of the patient based on site lab results (See Table 3 Dose modifications).		
Biochemistry**	• Sodium, Potassium , total calcium, magnesium • Albumin • Alkaline phosphatase • ASAT (SGOT), ALAT (SGPT) • Total bilirubin • Serum creatinine	Day 1 (+/-2) Cycles 1, 2, Day 1 (+3) of Cycle 3, 7, 11, and EOT, and as clinically indicated
	HbA1C	Day 1 (+3) of Cycle 3, 7, 11, and EOT
Drug compliance and dispensing	• Palbociclib/placebo bottles including any unused medication will be returned to the clinic for drug accountability. Drug accountability will be performed on Day 1 of each cycle prior to dispensing drug supply for the next cycle(s).	Day 1 (+/-2) at cycle 1, 2, Day 1 (+3) of Cycle 3, 4, 5, 7, 9, 11, 13

	Investigations during Treatment	Timing
Pharmaco-kinetics	• Plasma pk samples for drug-drug interaction(DDI) (sites not being prepared to collect pk samples will only be allowed to include patients planned for treatment with letrozole until these f 24 patient of a respective cohort are being included) - **sampling completed**	Several samples in cycle 1 and/or cycle 2 [only for the24 patients each receiving tamoxifen, and goserelin plus tamoxifen, or anastrozole]
	• plasma pk samples for drug exposure. **(sampling ongoing since mandatory for all patients)**	pre-dose Day 14 of cycle 1 and 2 [all patients]
Clinical disease assessment	Clinical disease assessment, relapse and survival status. Imaging (mammograph or MRI): Imaging should be performed at Cycle 7 and EOT.. In patients with mastectomy only contralateral mammography / MRI is required; patients with bilateral mastectomy should be assessed as per national guidelines recommended imaging examination.	cycle 7 and at EOT
Other Investigations	• Thoracic or abdominal CT / MRI, bone scans, x-rays, biopsies and others***	in case of symptoms suspect for disease progression or as clinically indicated
Cardiac monitoring**	• 12-lead ECG including automated calculation of PR interval, QT interval, RR interval, and QRS complex	Day 14 Cycle 1 and as clinically indicated

	Investigations during Treatment	Timing
Biomaterials	• 10 mL full blood for serum (mandatory) • 10 mL full blood for plasma (mandatory) • 20 ml full blood for detection of ctDNA (optional) • Formalin-fixed paraffin-embedded (FFPE) tumor tissue from metastasis in case of recurrence – upon occurance	Before cycle 7 and at EOT
Patient reported outcome and health economics –	• EORTC QLQ C30, • EORTC QLQ BR-23, • EORTC QLQ FA13 (Fatigue), • GAD7 patient self-rating mood scale • EQ-5D See Appendix 5-8 (21.5 – 21.8) Use of medical resources related to breast cancer and that may differ between trial arms****	Day 1 or (+/-2 days) of Cycle 1, 3, Day 1 or (+/ -7 days) of Cycle 5, 7, 9, 11, and EOT, and every 6 months until final primary endpoint analysis

* Toxicities will be recorded according to NCI-CTCAE v4 criteria with the maximum grade per cycle.

** Laboratory assessments will be performed whenever possible by the same laboratory throughout the study. Cycle 1/Day 1: Blood chemistry, hematology, 12-lead ECG and physical examination not required if acceptable screening assessment was performed within 7 days prior to randomization

***Every effort will be made to use the same instrumental examination from baseline until end of study treatment.

**** Medical resource use at the treating center should be recorded by study staff without involving the patient. Assessment of medical resource use by other health care providers and of lost resources (days of work etc.) should be based on patient interview

13.3 **Pharmacokinetic measurements**

All groups

Trough concentrations of palbociclib will be collected pre-dose on Day 14 of cycle 1 and 2 for all patients. These samples will be used for exposure/response analysis for safety and efficacy findings.

If these PK samples are not collected during the planned nominal visit/time, "make-up" samples can be drawn within the same cycle on Days 15 to 21, or in a later cycle on Days 14 to 21 providing that all planned doses of palbociclib in that cycle have been administered (ie no missed samples or dose interruptions) up until the PK collection day. The actual date and time of palbociclib administration for the most recent palbociclib dose before and the most recent dose after collection of the PK samples must be recorded in the study CRF.

Note: PK-DDI sampling as descbribed below is now complete, and communication that enrollment to PK-DDI cohorts was closed and further collections of PK-DDI samples should cease was communicated to sites via email and global newsletter.

In subsets of at least 24 evaluable patients each starting with the combination of tamoxifen and palbociclib/placebo, anastrozole and palbociclib/placebo, goserelin and tamoxifen and palbociclib/placebo plasma PK samples will be collected to explore DDI between palbociclib and the combination drug. Patients enrolled as a part of the DDI assessment subset who dropout of the study prior to completion of all planned PK collections for their respective treatment combination DDI assessment, may be replaced at the discretion of the Sponsor/Investigator to ensure that evaluable PK data is available from 24 patients within each endocrine treatment group. The PK sample handling and processing instructions are at the end of this section and further details can be found in the biomaterial management manual.

<u>Tamoxifen together with palbociclib/placebo patients</u>

In 24 patients receiving tamoxifen together with palbociclib/placebo plasma PK samples will be drawn on Cycle 2 Day 14 pre-dose and 2, 4, 6, 8, and 24 hours post-dose for DDI assessment. These samples will be analyzed for palbociclib, tamoxifen, 4-hydroxy-tamoxifen, N-desmethyltamoxifen, and endoxifen. The C_{max}, C_{min}, and $AUC_{(0-24)}$ of tamoxifen and its active metabolites will be compared between the palbociclip and placebo subgroups. The C_{max}, C_{min}, and $AUC_{(0-24)}$ of palbociclib will be compared with historical data. These data will be used to explore the potential two-way DDI between tamoxifen and palbociclib and the result will be used to inform dose adjustment if necessary after IDMC review of the DDI analysis.

If the planned PK samples are not collected during the planned nominal visit on Cycle 2 Day 14, then "make-up" samples can be drawn within the same cycle on Days 15 to 21, or in a later cycle on Days 14 to 21 providing that all planned doses of palbociclib and tamoxifen in that cycle have been administered (ie no missed samples or dose interruptions) up until the PK collection day. The actual date and time of administration for the most recent palbociclib and tamoxifen doses before and the most recent dose after collection of their respective PK samples must be recorded in the study CRF. Of note, the samples should be collected from the same dosing interval (ie if PK sampling starts with a pre-dose PK sample on Cycle 2 Day 18, then the 24hr post-dose sample should be drawn on Cycle 2 Day 19 and all planned samples drawn in between), and the 24 hours post-dose samples should be drawn prior to administration of the next dose.

Anastrozole together with palbociclib/placebo patients

In 24 patients receiving anastrozole together with palbociclib/placebo plasma PK samples will be drawn on Cycle 1 Day 14 pre-dose and 1, 2, 4, 6, 8, and 24 hours post-dose for DDI assessment. These samples will be analyzed for palbociclib and anastrozole. The C_{max}, C_{min}, and $AUC_{(0-24)}$ of anastrozole will be compared between the palbociclib and placebo subgroups. The C_{max}, C_{min}, and $AUC_{(0-24)}$ of palbociclib will be compared with historical data. These data will be used to explore the potential two-way DDI between anastrozole and palbociclib and the result will be used to inform dose adjustment if necessary after IDMC review of the DDI analysis. .

If the planned PK samples are not collected during the planned nominal visit on Cycle 1 Day 14, then "make-up" samples can be drawn within the same cycle on Days 15 to 21, or in a later cycle on Days 14 to 21 providing that all planned doses of palbociclib and anastrozole in that cycle have been administered (ie no missed samples or dose interruptions) up until the PK collection day. The actual date and time of administration for the most recent palbociclib and anastrozole doses before and the most recent dose after collection of their respective PK samples must be recorded in the study CRF. Of note, the samples should be collected from the same dosing interval (ie if PK sampling starts with a pre-dose PK sample on Cycle 1 Day 18, then the 24hr post-dose sample should be drawn on Cycle 1 Day 19 and all planned samples drawn in between), and the 24 hours post-dose samples should be drawn prior to administration of the next dose.

Goserelin and tamoxifen together with palbociclib/placebo

In 24 patients receiving goserelin and tamoxifen together with palbociclib/placebo, plasma PK samples will be drawn on Cycle 2 and Cycle 3 Days 1 and Day 14 pre-dose for DDI assessment. These samples will be analyzed for palbociclib, goserelin and tamoxifen. Concentrations of Goserelin and tamoxifen will be compared between the palbociclib and placebo subgroups. The concentrations of palbociclib will be compared with historical data.

These data will be used to explore the potential two-way DDI between goserelin and palbociclib and the result will be used to inform dose adjustment if necessary after IDMC review of the DDI analysis.

If the planned PK samples are not collected during the planned nominal visit, then "make-up" samples can be drawn in a later cycle on the same planned cycle Day (ie a Cycle 3 Day 1 sample can be made-up on Cycle 4 Day 1, and a Cycle 3 Day 14 sample can be made-up on Cycle 4 Day 14) providing that all planned doses of palbociclib, tamoxifen, and goserelin in that cycle (or the previous cycle in the case of Day 1 PK samples) have been administered (ie no missed samples or dose interruptions) up until the PK collection day. The actual date and time of administration for the most recent palbociclib, tamoxifen, and goserelin doses before and the most recent dose after collection of their respective PK samples must be recorded in the study CRF.

PK sample handling and processing instruction (Refer to the biomaterial management for details)

Collect 3 mL PK blood samples for each administered drug in the combination at each timepoint specified above and process each sample according to the procedure below:

1. Upon collection of blood samples in 3mL Lavender Top K2EDTA Tube, keep the blood PK samples on wet ice at all times prior to centrifugation.
2. Within 1 hour of collection, centrifuge the blood samples in the refrigerated centrifuges at approximately +4°C at about 1700xg for about 10 min.
3. Using a separate pipette for each time point, transfer the plasma samples into pre-labeled amber cryovials polypropylene tubes and stored at the following temperatures per analyte: the tamoxifen, anastrozole and palbociclib samples should be stored at -20°C and the goserelin samples at -80°C .
4. As much as practical, keep the blood and the plasma samples away from direct sunlight and unfiltered lab light.
5. Ship the samples on dry ice to the biobank as per study team request.

Sites not being prepared to collect PK samples for DDI Assessment will only be allowed to include patients planned for treatment with letrozole until the 24 patients of a respective cohort are being accrued. Inclusion of patients into the study will not be put on hold to wait for the results of these Pk analyses.

13.4 Patient Reported Outcomes (PRO) and health economics

Patients reported outcome and health economic analyses: data will be captured using the following questionnaires: the EORTC QLQ-C30, the breast cancer module QLQ-BR23, QLQ

fatigue, GAD7 patient self-rating mood scale and the EQ-5d instruments. Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of absolute scores and their changes from baseline will be summarized at each assessment time point for the 2 treatment arms. Only patients with a baseline assessment and at least one post-baseline assessment will be included in this analysis. Repeated-measures mixed-effects models will be used to explore the treatment effect changes over time and treatment-by-time interaction. Details on distribution, advising patients and analysis will be provided in the statistical analysis plan.

13.4.1 EORTC QLQ-C30, EORTC QLQ-FA13, QLQ-BR23

The EORTC QLQ-C30 is a validated and reliable self-report measure [114 115 116]) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social); three symptom scales (fatigue; nausea, vomiting, and pain; and the global health/quality of life) and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales. The fatigue module has been developed for use in all diagnoses, stages of the disease and treatment settings. It is measuring cancer related fatigue based on a multidimensional approach including physical, emotional and cognitive aspects of fatigue. One global item is assessing the interference of fatigue with activities of daily living. FA-13 (reduced version with 13 items to be used in combination with EORTC QLQ-C30, Weis, J. 2009;) The QLQ-BR23 breast cancer module is meant for use among patients varying in disease stage and treatment modality.[117] The module comprises 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy, and hormonal treatment), body image, sexual functioning, and future perspective. The breast cancer module incorporates five multiple-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image, and sexual functioning. In addition, single items assess sexual enjoyment, hair loss, and future perspective. The QLQ-C30 and QLQ-BR23 take 10 to 15 minutes to complete.

13.4.2 EQ-5D

The EQ-5D is a widely used, preference-based measure of health related quality of life (utility) that is frequently used as a basis for calculating quality-adjusted life years (QALY) and for conducting health economic evaluation studies[118 119]. The EQ-5D measures five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), offering three answer categories for each[120 121]. Resulting health states are combined with country-specific value sets, derived from population-based studies, to calculate utility. In addition, a visual analogue scale (VAS) allows individuals to directly rate their self-perceived overall health state. It takes about 5 minutes to complete the EQ-5D.

Health economics: medical resource use related to breast cancer and that may differ between trial arms will be collected as a basis for cost analysis and health economic evaluation. Medical resource use at the treating center will be recorded by study staff

without involving the patient. Assessment of medical resource use accrued with other health care providers and of lost resources (lost days of work etc.) will be based on patient interviews and/or patient diaries. It is estimated that during the treatment period, the additional time requirement will be 15 minutes of patient and staff time per clinical visit. During the follow-up period, the expected time requirement is an 20 minutes per assessment time point.

Details of the cost analyses and health economic evaluation will be described in a Health Economic Analysis Plan. In brief, cost differences between treatment strategies will be assessed for the final iDFS (and interim OS) analysis time point (QIV 2018), for the final OS analysis time point (QIV 2021), and with a lifelong time horizon based on extrapolation. Incremental cost-effectiveness, expressed as cost per QALY gained, will be estimated based on the data available at the final iDFS and final OS analysis time points, using a lifelong time horizon. Supporting analyses may be added.

Given the specifics of health economic analysis, some points must be noted: Approaches to analysis will follow the health economic state-of-the-art, which may evolve until the analyses are due. Assessments of cost and cost-effectiveness will make use of clinical, utility and medical resource use data collected within the PENELOPE tiral. Unit cost estimates and potentially a limited number of additional parameters will come from external sources. Health economic analysis is always country-specific; countries for which the analyses will be performed, and perspectives of cost assessment, remain to be specified. One option will be to select the largest recruiters into the trial. Consistency of medical resource use across centers and countries will be assessed. If related issues are detected, the use of medical resource use data may need to be restricted to a subset of centers, with an implication of increased statistical uncertainty. If the recording of medical resource use data showed to be only partially feasible (e.g. due to issues with patient compliance), health economic methodology would allow to implement approximate solutions; related limitations of validity would be discussed. Depending on the clinical results of the trial (e.g. if no clinical advantage palbociclib is demonstrated), some of the planned analyses may become obsolete.

13.4.3 General Anxiety Disorder-7 (GAD-7)

The General Anxiety Disorder-7 (GAD-7) will be collected with baseline and to aid in the identification and severity assessment of potential mood alterations. The GAD-7 are validated (Kroenke 2001, Spitzer 2006, Spitzer 1999), patient self-administered questionnaires developed for use in clinical practices.

The GAD-7 is a one-dimensional questionnaire consisting of 7 questions. Patients are asked to indicate how often, over the past 2 weeks, they have been bothered by each of the seven core symptoms of generalized anxiety disorder as referenced in the DSM IV. Response options are ‘‘not at all,’’ ‘‘several days,’’ ‘‘more than half the days,’’ and ‘‘nearly every day,’’ scored as 0, 1, 2, and 3, respectively. The sum of all seven questions calculate the total GAD-7 score. Therefore, GAD-7 scores range from 0 to 21.

Toxicity grading based on anxiety questionnaire scores

GAD-7 (anxiety)		
Score	Severity	Grading
0-4	None	Normal
5-9	Mild	Grade 1
10-14	Moderate	Grade 2
≥ 15	Severe	Grade 3

Score Severity Grading

Over the last 2 weeks, how often have you been bothered by the following problems? (Use "✔" to indicate your answer")	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
(For office coding: Total Score T	_____	= _____	+ _____	+ _____)

*** Note: The grading guidance above may be overruled at the discretion of a psychiatrist performing a consult.**

13.5 Collection of Biomaterials

- Collection of formalin-fixed paraffin-embedded (FFPE) tumor tissue block from diagnostic core before start of chemotherapy and at surgery is mandatory. For central review at least 3 cores should be sent to the central pathology laboratory.
- One serum sample (out of 10 mL full blood) should be collected before start study treatment, at day 1 of the 7th cycle and at EOT (mandatory). Serum preparation should be performed as follows: collect 10 ml of peripheral blood in an S-Monovette (Sarstedt; monovette contains granula-bound coagulation agent), invert the tube to mix blood with coagulation agent and leave the sample 20 to 30 min at room temperature. After 20 to 30 min, the clotting of the blood is completed. Please centrifuge the sample for 15 min at 1500g and transfer the clear or yellow supernatant (upper phase/layer = serum) into the 5 fresh tubes supplied. For tube labeling use adhesive labels provided with the lab kit. The serum samples must be frozen immediately at -20°C to -80°C. The samples frozen at -20°C to -80°C will be stored at the center. Samples will be picked up by a courier service.
- For plasma isolation 10ml of peripheral blood should be collected before start of study treatment, at day 1 of the 7th cycle and at EOT (mandatory). Peripheral blood will be sampled in an EDTA test tube and inverted for several times (5x). After centrifugation for 15 min at 1500g, the plasma can be collected from the supernatant and transferred into 5 fresh tubes. The samples must be frozen immediately at -20^{o}C to -80^{o}C and stored at the center until pick up by a courier service.
- One full blood sample (10 mL) of each patient will be collected preferably before start of study treatment (but can be also collected later) for SNP analysis (mandatory). The samples must be stored frozen at -20°C to -80°C at the center.
- Additional optional full blood sample (20 mL) will be collected before study treatment, at day 1 of the 7th cycle, at EOT and within 4 weeks after confirmation of progressive disease for the analysis circulating DNA (ctDNA).

All technical and transportation devices (material for blood and serum sampling and packaging) will be provided by the GBG.

13.6 Biomarker analysis

Specific information and guideline on the detection of centrally assessed biomarkers before randomization or exploratory detected biomarkers after randomization are available upon request if required.

13.7 End of Treatment (EOT)

The regular end of treatment for a patient is defined as 30 days after the end of the last capsule intake of palbociclib/placebo.

13.8 **Follow-up Period**

Post-Treatment Follow-Up will be assessed according to ASCO-guidelines [122]. Patients who discontinue study treatment for any reason other than objective relapse of disease or death will continue to have tumor assessments performed according to ASCO guidelines. See Tumor Assessment Requirements Flowchart for details. For patients who discontinue study treatment due to objective disease progression, survival data (i.e., patient status, onset and type of new anticancer therapy will still be collected approximately every 6 months (+/- 14 days) from the last dose of study treatment.

Following the EoT visit, clinical disease assessment will be performed (in patients who have not experienced an iDFS event), and survival status will be collected in all patients (telephone contact or contact in writing with the patient or treating physician is acceptable) twice a year after the last dose of study treatment. Imaging tests have to be performed according to national guidelines for follow up and in case of symptoms suspicious for locoregional or distant relapse but at leaset once a year. Information will be collected on date and site of first non-invasive local recurrence, first invasive local recurrence, first contralateral breast recurrence, first regional recurrence, first distant recurrence, first palliative endocrine, first palliative cytotoxic (+/- targeted) treatment, date and cause of deaths as well as date and diagnosis of secondary malignancies, as well as every serious adverse reaction related to palbociclib/placebo.

In case of disease progression it is recommended to confirm diagnosis by histological examination. A FFPE tumor tissue block from the metastatic lesion should be provided to GBG.

Newly occurred serious adverse reactions (SARs) have to be documented on the SAE form and have to be sent to the Sponsor within 24 h after becoming aware of the event.

Participating patients are recommended to be registered in the GBG self-reporting registry (if allowed by national regulations) that will allow further follow up and long-term efficacy evaluations beyond the end of the study.

13.9 **Treatment Discontinuation of Individual Patient**

If a patient shows one of the following reasons palbociclib/placebo treatment has to be discontinued from study treatment:

- Detection of local, regional or distant invasive recurrence breast cancer,
- Unacceptable toxicity according to investigators decision
- Detection of any secondary malignancy
- Patients request or non-compliance.

The reason and date of discontinuation for all patients will be documented on the Case Report Form (e.g. progressive disease, death, adverse event, withdrawal of consent, lost to follow-up, etc.).

The investigator will attempt to complete all discharge procedures at the time of discontinuation of palbociclib/placebo treatment. The procedures have to be documented in the CRF.

13.10 **End of Study (EOS)**

13.10.1 Regular End of Study

No interventional procedures after final iDFS (and interim OS) analysis. All patients will be contacted by telephone before the database lock. The end of study is defined with evaluation of the primary objective. Planned end of study is QIII 2020. Survival and Relapse assessments will continue post study.

13.10.2 Premature Termination of Study

The study may be terminated prematurely for safety reasons, slow accrual, or upcoming new data impairing the relevance of the study objective by the GBG Forschungs GmbH as the sponsor or the protocol board. The Independent Data Monitoring Committee will provide advice. The sponsor is allowed to close the trial for any reason at any time. A decision to prematurely terminate the study is binding to all investigators of all study sites. Responsible ethics committees and regulatory authorities will be informed about the reason(s) and time of termination according to the applicable laws and regulations.

If the study is terminated prematurely, all investigators have to inform their patients and take care of appropriate follow-up and further treatment of the patients.

13.10.3 Premature Termination of Study at a Particular Study Site

The GBG Forschungs GmbH as the sponsor reserves the right to discontinue the study at a particular study site at any time. The reasons will be discussed with the investigator.

The GBG Forschungs GmbH may terminate this study in one particular study site for one of the following reasons:

Non-compliance with GCP and/or regulatory requirements.

Insufficient number of recruited patients.

False documentation in the CRF due to carelessness or deliberately.

Inadequate co-operation with GBG Forschungs GmbH or its representatives.

The Investigator request to close of his/her study site.

If the study is prematurely terminated in a study site, the responsible investigators have to inform their patients and take care of appropriate follow-up and further treatment of

the patients. The responsible ethics committee and regulatory authorities will be informed about the reason and time of termination according to the applicable laws and regulations.

14. DATA QUALITY ASSURANCE

14.1 Data Management and Documentation

Data management and monitoring will be carried out by the GBG Forschungs GmbH. Data management refers to eCRF design, database and application hosting and data validation.

All CRF data will be entered into the trial database using the MedCODES® application, which will perform automated plausibility and value range checks before committing the data to the database. As soon as a Case Report Form is committed to the database it can no longer be edited or deleted by the investigator. Committed data, other than baseline, can be changed by the investigator as long as it is not monitored. Any changes made by the investigator are reviewed by data management. Once data is monitored, the investigator is not allowed to make any changes without a query.

CRF data will be reviewed by a data entry clerk and queries created for every data field that do not match the trial guidelines. These queries will be forwarded to be resolved (within the MedCODES® application) to the center. Resolved queries will be checked by a data entry clerk and closed or if necessary requeried.

The patient baseline and registration eCRFs will be checked for eligibility manually and using programmed checks. Visual and computerized methods of data validation are applied in order to ensure accurate, consistent and reliable data for the subsequent statistical analysis. These procedures detect out-of-range values, contradictory data, and abnormal changes over time, and possible protocol violations.

As soon as all data is stored in the trial database and all queries are closed, patient data entry in MedCODES® is stopped, all patients (CRF) are set to “End Status”, any data changes in MedCODES® are stopped. The database is locked to any kind of manipulation and then handed over to the Statistics Department. Prior to statistical analysis, concomitant medications entered into the database will be coded using the WHO Drug Dictionary,. Medical history, adverse events, cause of death, antineoplastic surgeries, procedures or nondrug therapies will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Pseudonymisation

In order to keep patient data confidential and for safeguarding the privileged doctor patient relationship, each participating patient will be assigned a unique GBG reference number. This reference number consists of a trial specific prefix and a unique randomization number from a prepared block of numbers.

The pseudonym, instead of the true patient identity, is used in all communication between the trial site and the GBG Forschungs GmbH.

User Access Control

Every user is provided with a personal user name and password. Every user is assigned to a user group, which represents their role in the MedCODES® application.

Access control is based on user name, group and place of work (e.g. center or the GBG Headquarters). Users can only access those datasets necessary for them to fulfill their role in the CRF workflow ("need to know basis").

14.2 Monitoring and Source Data Verification

All source data verification (SDV) is conducted according to GBG monitoring standard operations procedures (SOP).

The investigator must permit the monitor, the sponsor's internal auditors and representatives from the regulatory authorities to inspect all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

After logging in to the MedCODES® application, the monitor chooses a trial center (their current location) and a trial. Source data verification is then performed by consulting the patient file. In case of discrepancies the monitor creates queries which must be solved by the center.

14.3 Computer Systems

All data are collected and stored using the MedCODES® application. The MedCODES® application is based on an Apache 2.4 / PHP 5.5 application server and a MySQL 5.6 database backend.

Due to the nature of the MedCODES® application, the trial centers must be equipped with computer terminals with online access and current versions of Microsoft Internet Explorer, Mozilla Firefox or Apple Safari. JavaScript execution must be enabled with the web browser.

15. STATISTICS

The statistical analysis of the present study is performed in accordance with the principles stated in the Consensus Guideline E9 (Statistical Principles for Clinical Trials) of the International Conference on Harmonization (ICH).

15.1 Disposition of patient

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients, who have been allocated to treatment with palbociclib or placebo of palbociclib based on the randomization process. It will consist of all patients with randomization number and recorded in the computerized system database and regardless of whether the treatment was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the **All randomized and treated patients (SP)** population.

For patient study status, the total number of patients for each one of the following categories will be presented:

Screened patients

Randomized patients

Randomized and treated patients

Patients who discontinued study treatment by main reason for permanent treatment discontinuation.

15.2 Analysis populations

Randomized patients consist of all patients who have given their written informed consent and for whom there is confirmation of successful allocation of a randomization number through the web-based data collection interface.

Intent to treat (ITT) efficacy population: all randomized patients (including those not starting treatment). This population provides the basis for the main efficacy analyses. Patients will be analyzed according to the treatment group they were randomized to.

Evaluable patients (EP) efficacy population: subset of the ITT population, this population includes all treated patients with at least 80% of the planned number of doses of palbociclib/placebo. This population is for supportive efficacy analyses. Patients will be analyzed according to the treatment group they were randomized to.

All randomized and treated patients safety (SP) population: all randomized patients (excluding those not starting treatment). Patients will be analyzed according to the treatment actually received. This is the only population for all safety analyses.

In addition:

Not randomized but treated patients will not be part of the safety population, but their safety data will be presented separately.

Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.

For patients receiving palbociclib and placebo during the trial, the treatment group allocation for as-treated analysis will be the palbociclib arm.

Translational Research sub-study population: a subset of randomized and treated patients with available molecular-biological parameters before first study drug administration. All analyses using this population will be based on the treatment received.

Major protocol violations according to the sponsor guideline are applicable and made available to sites for referencing Major protocol violations leading to exclusions from the available subset will be defined in the statistical analysis plan.

15.3 Sample Size Determination

Sample size was determined based on the analysis of the primary endpoint, iDFS. The sample size was calculated based on the following assumptions:

- Time to iDFS event follows an exponential distribution.
- 3-year iDFS rates for placebo arm and for the palbociclib arm are 0.77 and 0.836, respectively. The rates are equivalent to a HR (palbociclib/ placebo) of 0.685.

Based on these assumptions, a minimal number of 255 iDFS events will be required to give 85% power to detect a HR (palbociclib/ placebo) of 0.685 at the 0.05 significance level (2-sided) on iDFS using a stratified log-rank test.

Assuming time to dropout follows exponential distribution with a common hazard rate (0.04383 subjects per year) for both arms. Applying a 1:1 randomization and a non-uniform enrollment rate of 40 subjects per month at the peak, it was estimated that 1100 subjects will need to be enrolled. The total enrollment period is estimated to be 3.6 years.

The final analysis will take place when 255 iDFS events are observed which is estimated to occur about 6.5 years after first patient.

Power calculation is also done for the secondary endpoint of iDFS excluding second primary of non-breast cancer. Assuming that not more than 15% of iDFS events are second primary of non-breast cancer, there is 79% power to detect statistical significance between the 2 arms with a 2-sided significance level of 0.05.

Rationale of assumptions on sample size determination

Estimation of 3-year iDFS rate was performed on the basis of a metadatabase containing 2659 HR+/Her2- patients who received neoadjuvant therapy (about 18-24 weeks), surgery (average period of around 6 weeks after last cycle of chemotherapy) and radiation (about 6 weeks). In the PENELOPE^{B} study patients will be randomized after radiation or rehabilitation, if applicable, which is estimated to be approximately 9 months after start of neoadjuvant chemotherapy. Given these assumptions a 3-year iDFS rate of 0.77 was estimated for the control arm of patients with CPS-EG score >= 3 or CPS-EG score = 2 and ypN+. The assumption of exponential distribution on time-to-iDFS event for the control arm may affect the duration of study. This assumption cannot be assessed due to lack of patient-level data on surgery date.

15.4 Treatment Stratification

Randomization will be stratified using block randomization by:

- histological lymph node status at surgery (ypN 0-1 vs ypN2-3)
- age at first diagnosis (<=50 vs >50 yrs)
- Ki-67 measured (>15% vs <=15%)
- global region of participating site (Asian vs non Asian)
- risk status (CPS-EG Score >=3 vs CPS-EG Score = 2 and ypN+)

15.5 Statistical Analyses

15.5.1 Analyses of primary and secondary endpoints

Analysis of Primary Endpoint

Primary efficacy endpoint is invasive disease-free survival (iDFS) which is defined according to Hudis as the time period between randomization and first event (ipsi- or contralateral invasive in-breast or loco-regional recurrence, distant recurrence, death from breast cancer, death from non-breast cancer cause, death from unknown cause, invasive contralateral breast cancer, second primary invasive cancer (non-breast)).

The primary analysis for iDFS will be the comparison between treatment arms in the ITT population with a 2-sided stratified log-rank test at the overall significance level 0.05. The factors used in the stratified log-rank test will be histological lymphnode status at surgery (ypN 0-1 vs ypN 2-3), age at first diagnosis (<=50 vs >50 yrs), Ki-67 (>15% vs <=15%), and risk

status (CPS-EG score >= 3 vs. CPS-EG score = 2 and ypN+). Global region will not be included. The nominal significance level for the final analysis of iDFS is 0.0463 because of the two planned interim analyses. In addition, iDFS curve will be estimated in each treatment arm using the Kaplan-Meier method. Cox regression model stratified by the factors used in the stratified log-rank test will be used to estimate the treatment hazard ratio. The iDFS rates at 3 years will also be estimated for each arm.

Final efficacy analysis

Final analysis of the primary endpoint and secondary efficacy endpoints (except for OS) will be conducted when the target number of iDFS events for the final analysis have been observed. The minimum number of iDFS events is 255. Due to the adaptive design of the trial this number can be increased to a maximum of 290 iDFS events depending on the result of the efficacy interim analysis. The final analysis is estimated to be performed approximately 6.5 years after first patient randomized.

Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- iDFS excluding second primary of non-breast cancers
- overall survival (OS)
- distant disease free survival (DDFS)
- locoregional recurrences-free (LRRFS) survival
- iDFS per treatment group in patients with luminal-B tumors as determined by PAM50.

Overall survival (OS) is defined as the time period between randomization and death of any cause. An interim OS analysis will be conducted at the time of final iDFS analysis and final OS analysis will be conducted at a later time after the final analysis for iDFS endpoint. Details will be described in Statistical Analysis Plan.

Locoregional recurrences-free survival (LRRFS) is defined as the time period between randomization and diagnosis of any loco-regional (ipsilateral breast (invasive or DCIS), local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer or death due to any cause whichever occurs first. Distant disease free survival (DDFS) is defined as the time period between randomization and diagnosis of any distant recurrence of disease, any second primary invasive cancer (non-breast) or death due to any cause whichever occurs first. LRRFS and DDFS will be analyzed at the time of final iDFS analysis.

Time-to-event curves will be estimated using the Kaplan-Meier method and compared between 2 arms with a two-sided stratified log-rank test. Univariate Cox-proportional hazards model will be used to calculate hazard ratios for the overall population as well as for subgroups predefined by the stratification factors.

Multivariate Cox-proportional hazards model will be performed for event free data, to adjust for all stratification factors, as well as clinical stage before neoadjuvant chemotherapy, pathological stage after neoadjuvant chemotherapy, and grade.

Analysis of Other Endpoints

Tolerability and Safety: Descriptive statistics for the 2 treatments will be given on the number of patients whose treatment had to be reduced, delayed or permanently stopped. The reason for termination includes aspects of efficacy (e.g. termination due to tumor progression), safety (e.g. termination due to adverse events) and compliance (e.g. 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. Safety by toxicity grades will be defined by the NCI-CTCAE v4.0.

Patients reported outcome and health economic analyses: data will be captured using the following questionnaires: the EORTC QLQ-C30, the breast cancer module QLQ-BR23, QLQ fatigue, GAD7 patient self-rating mood scale and the EQ-5d instruments. Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of absolute scores and their changes from baseline will be summarized at each assessment time point for the 2 treatment arms. Only patients with a baseline assessment and at least one post-baseline assessment will be included in this analysis. Repeated-measures mixed-effects models will be used to explore the treatment effect changes over time and treatment-by-time interaction.

*Translational research***:** Exploratory analyses will be performed to identify possible relationships between biomarkers and iDFS and OS. Patients with missing biomarker data will not be included in the respective analysis

15.5.2 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the *All randomized and treated patients population.*

15.5.3 Extent of investigational medicinal product exposure

Duration of palbociclib/Placebo exposure is defined as: last dose date – first dose date + 7 days regardless of unplanned intermittent discontinuations.

The overall extent of exposure will be assessed for each patient as:

- Duration of exposure
- Total number of cycles (K)

Dose information:

The actual dose received

Cumulative dose (mg) defined at cycle k as the sum of all doses from cycle 1 to and including cycle k, where k is based on Investigator's report.

The actual dose intensity (ADI) is defined as the cumulative dose divided by the number of weeks on treatment (mg/week) including delays.

The relative dose intensity (RDI) is defined as the ratio of the actual dose intensity to the planned dose intensity. RDI, as an indicator of the feasibility of the chosen schedule of administration.

Dose reduction and reason for dose reduction: Dose reduction will be derived using the definition provided in the protocol compared to the previous dose. For the second and subsequent cycles, a dose is deemed to have been reduced if the dose level a patient receives is lower than the previous actual dose level.

Dose delays: A cycle is deemed to have been delayed if start date of the current cycle – start date of previous cycle > 3.

15.5.4 Analysis of Adverse Events

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the randomized and treated patient populations.

The grade will be taken into account in the summaries. For patients with multiple occurrences of the same event, the maximum grade is used.

Sorting within tables should ensure same presentation for the set of all AEs within the observation period.

Adverse event incidence tables will be presented by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the All randomized and treated patients population within each treatment group.

15.5.5 Analyses of laboratory variables

The baseline value is defined as the last available value before randomization.

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI-common terminology criteria (version 4.0).

The number of patients with abnormal laboratory tests at baseline (grade ≥1) will be presented by grade. The frequency of patients in each grade of laboratory test during

treatment will be summarized. For patients with multiple occurrences of the same laboratory variable during the treatment, the maximum grade (worst) per patient will be used. When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with grade 3-4 of abnormal laboratory tests.

For the non-NCI gradable parameters, out-of-normal laboratory range value analyses will be performed.

15.5.6 Translational research analyses

The analyses will be defined in the separate Statistical Analysis Plan.

15.5.7 Interim Analysis for Safety

Safety interim analysis (SIA) reviewed by the IDMC have a special focus on safety and reasons for treatment discontinuations (including progressive disease) and are scheduled regarding the number of patients having completed 2 cycles of treatment or discontinued study treatment prematurely: after the first 25 patients, two more SIA after approximately further 50 patients each, then after further 50 patients and whenever the next 300 patients have completed 2 cycles or discontinued study treatment prematurely. SIA frequency may be adjusted due to the IDMCs recommendations.

Ad-hoc IDMC meetings may also be held if a significant safety issue or issue deemed important for discussion arise on this or any other palbociclib study. After each meeting, the IDMC will advise the and the Sponsor's representative on the further conduct of the trial.

In subsets of 24 at least evaluable patients each starting with the combination of palbociclib/placebo and tamoxifen, palbociclib and anastrozole, and palbociclib/placebo and goserelin and tamoxifen plasma PK samples will be collected to explore DDI between palbociclib and the combination drug. No significant DDI between Palbociclib and Letrozole were observed and no samples need to be collected to explore DDI for the Letrozole combination.

A PK unblinding plan will allow for review of the PK data prior to completion of the trial without unblinding the trial. The PK unblinding will be applied once all planned PK samples from at least 24 evaluable patients of each assessed combination have been collected. PK parameter analysis will proceed according to the PK analysis plan with results provided to the IDMC for review. The study will continue while PK analysis and data review are ongoing. Details of the analysis (along with other safety data included in the early safety review) will be provided in the IDMC charter.

15.5.8 Interim Analysis for Efficacy

Two efficacy interim analyses (EIA) will be performed in the study. O'Brien – Fleming type stopping boundaries based on the Lan-DeMets spending function will be applied. Futility criteria are not used to calculate the nominal alphas (non-binding method) in order to control the overall Type-I-error.

The objectives of the first EIA will be:

- To re-estimate the sample size.
- To assess safety, including any unexpected toxicity.
- To allow for early stopping of the trial due to futility.

The objectives of the second EIA will be:

- To assess safety, including any unexpected toxicity.
- To allow for early stopping of the trial due to futility.
- To allow for early stopping of the trial due to overwhelming efficacy.

The first EIA was originally planned to be performed after the first 85 events (1/3 of the total events) have occurred or prior to the last patient randomized to allow for the continuation of the enrollment in case of SSR. According to an estimation in February 2017 the planned fraction of events would have occurred one month after last patient randomized. It was estimated that approximately two months are required to perform the EIA and to implement potential changes. Therefore, the EIA is scheduled to be performed in April 2017.

The second EIA will be performed on the basis of 2/3 of the total events. It was estimated that 2/3 of 255 events (170 events) will have occurred <5 years from the first patient randomized. In case of sample size re-estimation, 2/3 of 290 events (194 events) must have been documented, which is estimated to have occurred 5.1 years from first patient randomized.

The unblinded results of the EIA will be provided to the IDMC to receive recommendation regarding the efficacy interim analysis' objectives. All staff at GBG will remain blinded to the treatment allocation of the patients with exception of the independent statistician (unblinded statistician).

The following table displays the decision rules regarding the objectives of the two EIA and the final analysis.

Analysis	Time / Information Fraction	Number of events min/max	Futility (HR)	Sample size re-estimation	Efficacy (α-level)
1st EIA	April 2017	67	≥1.0	Yes	<0.0002
2nd EIA	2/3	170/194	≥0.90	No	<0.0120
FA*	3/3	255/290	N/A	N/A	<0.0463

* Final Analysis

The actual nominal α levels for the EIA and for the final analysis will depend on the fraction of total events occurred at the time of analysis, in order to control the overall type I error for the endpoint of iDFS.

At EIA statistical hypothesis tests will be performed only for the primary efficacy parameter, iDFS. The secondary endpoint of iDFS excluding second primary of non-breast cancer will also be taken into consideration when performing sample size re-estimation (SSR).

Cui, Hung and Wang method will be used for adaptive sample size modification. The decision about SSR will be made on the basis of the favorable zone concept by Mehta and Pocock. In case the conditional power calculated on the basis of the efficacy interim analysis' treatment effect fell in the favorable zone, increase of sample size to the maximum of 1250 patients and increase of the number of iDFS events to the maximum of 290 events is planned. The definition of the favorable zone is only laid down in the addendum to the IDMC charter and must be kept secret to avoid "reverse engineering" of the treatment effect.

15.5.9 Further Analysis after the End of the Study

Final survival will be analyzed 3 years after the final analysis on iDFS. Survival time in each treatment group will be estimated with the Kaplan-Meier product-limit method and will be reported together with the two-sided 95% confidence interval. The log-rank test will be performed to compare overall survival between the two treatment groups.

The multivariate Cox proportional hazards model will be used for all efficacy endpoints in order to adjust for the major prognostic factors.

16. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

16.1 IDMC Members and Mission

In addition to the Protocol Board, the Independent Data Monitoring Committee (IDMC) of the GBG reviews and monitors the conduct of the trial. The IDMC consists of five members, three medical oncologists, one biometrician and a patients advocate. An ad hoc member experienced in CDK inhibitors will join each meeting via telefon conference support the IDMC. The members are independent of the trial and familiar with the methodology of oncology trials. They are aware of the dangers of conclusions based on immature data and have agreed with the design and the goals of this protocol. IDMC meetings are held at least every six months or as stated in section 15.5.4. The mission of the IDMC is to ensure the ethical conduct of the trial and to protect patients' safety interests in this study. The work of the IDMC will further specified in a separate charter.

16.2 **Recommendations of the IDMC**

After each meeting, the IDMC will provide the Protocol Board with a written recommendation to either modify the trial (with reasons), or discontinue the trial (with reasons), or make the interim safety and efficacy results of the trial public (with reasons), or continue the trial unchanged. The final decision to amend the protocol or to discontinue the trial will be taken only by the International Steering Committee.

16.3 **Early Termination of the Trial**

Early termination of the trial will be considered by the International Steering Committee based on suggestion of the IDMC if less than 50 patients are recruited within 12 months, unsatisfactory toxicity or compliance.

17. ADVERSE EVENTS

Patients will be instructed by the investigator to report the occurrence of any adverse event.

17.1 **Adverse Event**

An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. It also includes any undesirable clinical or laboratory changes which does not commonly occur in the patient.

The study Investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0)

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI-common terminology criteria (version 4.0). (see section 15.5.5) .

In case serum creatinine increase fulfills criteria to be reported as AE, the cause of the renal function impairment should be reported and the renal function impairment should be considered in the grade of the reported AE according to NCI-CTCAE version 4.0. If no cause can be identified and creatinine increase is considered serious or has an action taken on study treatment (dose reduction, dose delay, dose interruption or permanent discontinuation), the “creatinine increase” term should be preferred rather than the “renal failure” term.

Any case of renal function impairment should be documented at least by a creatinine value and creatinine clearance. Tests will be repeated until recovery or stabilization and all results will be recorded in the e-CRF. Any complementary exams made to explore renal function or

the cause of renal failure should be reported in the e-CRF and product contrast administration for CT scan should be recorded in concomitant medication.

17.2 **Adverse Reaction**

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). 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 basis 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.

Pfizer has agreed to inform GBG in an expedited manner of any Suspected, Unexpected and Serious Adverse Reactions (SUSAR) for the product, observed at any time after a subject has received the study drug.

The impact of any report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review (including, but not limited to, an increase in the frequency of expected serious adverse effects, events in connection with the study execution or the development of the study drug that can potentially affect the safety of the affected persons, significant safety findings from animal or in vitro studies), as well as any appropriate action in response, will be promptly notified to GBG.

17.3 **Serious Adverse Event/Serious Adverse Reaction**

A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires or prolongs hospitalization, results in persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event from the time the patient signs the informed consent. Important medical events are those which may not be immediately life-threatening, but are clearly of major clinical significance.

Pregnancy and AEs of special interest (see Section 17.5) must also be documented on the serious adverse event form.

Exceptions:

Progression of the malignancy during study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal and death occurred before EOT. Thereafter death due to disease progression has not to be reported as SAE. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE.

Hospitalization which is due solely to a planned study visit and without prolongation does not constitute a Serious Adverse Event.

An overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background does not need to be handled/documented as a Serious Adverse Event.

17.4 Suspected Unexpected Serious Adverse Reactions

All unexpected serious adverse events judged by either the investigator or the GBG Forschungs GmbH as the sponsor to have a reasonable suspected causal relationship to an investigational or an accompanying medicinal product qualify as suspected unexpected serious adverse reactions (SUSAR). Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

All Suspected Serious Adverse Reactions (SAR) must be reported to the GBG Forschungs GmbH as the sponsor regardless of the time which has elapsed during the clinical trial (treatment and follow-up phase).

17.5 Adverse Events of Special Interest

For AESIs the Sponsor will be informed immediately (ie, within 1 working day), as per the SAE notification instructions described in Section 17.7, even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF.

17.5.1 Pregnancy:

Pregnancy occurring in a female patient included in the clinical trial. Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.

In the event of pregnancy, IMP must be discontinued.

Follow-up of the pregnancy is mandatory until the outcome has been determined.

17.5.2 Relevant overdose with IMP:

A relevant overdose (accidental or intentional) with the IMP is an event suspected / identified by the Investigator or spontaneously notified by the patient and defined as the intake of more than 23 capsules during a cycle (28 days) or more than 2 capsules within 24h.

It has to be reported within one working day as an AESI using the SAE reporting form.

17.5.3 Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold for laboratory abnormalities in the case of potential drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

Patients with AST or ALT and total bilirubin baseline values ***within the normal range*** who subsequently present with AST or ALT ≥3 times the upper limit of normal (X ULN) **concurrent with** a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.

For patients with ***preexisting*** ALT **OR** AST **OR** total bilirubin values ***above*** the upper limit of normal, the following threshold values should be used in the definition mentioned above:

- For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

Concurrent with

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased twice the baseline value.

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the

investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

17.6 **Death on Study**

Any death occurring during the active treatment part of the study and within 30 days following the last treatment must be reported to the GBG Forschungs GmbH as the sponsor within 24 hours, regardless of the relation to study drug(s), and has to be reported on the death report form section of the CRF.

The cause of death should be documented (cancer-related, treatment-related, cancer- and treatment-unrelated). Autopsy reports should be collected whenever possible and sent to the GBG Forschungs GmbH.

Deaths that occur due to tumor progression do not have to be reported as a SAE unless they occurred before EOT.

Deaths after the end of study which are considered to be related to study treatment have to be reported as SARs.

To the extent feasible sufficient information including relevant laboratory values, ECG, scan, biopsy or autopsy results must be provided by the investigator in the SAE narrative (even if investigator determines the SAE is not related) so as to permit an independent causality assessment by a Health Authority.

17.7 **SAE and AESI Reporting**

Refer to section 17.3 for the definition of a SAE and section 17.5 for definition of an AESI. All SAEs/AESI from the time the patient had the first dose of the investigational medicinal product (IMP) through 30 days following the last administration of IMP must be reported according to the procedure described below. All SAE regardless of timing must be reported, if considered related to study drug.

Likewise, progression of a patient's underlying condition leading to one of the above should also not be reported as a serious adverse event, but documented as primary study endpoint. (See also Section 17.3).

Address for reports on SAE/AESI (within 24 hours from documented awareness):

GBG Forschungs GmbH Martin-Behaim-Straße 12 63263 Neu-Isenburg Germany	Phone: +49 (0) 6102 / 7480-0	Via MedCODES or alternatively via Fax: + 49 (0) 6102 / 7480-440

The GBG will report all SAEs and AESIs immediately t to the pharmaceutical manufacturer.

All SAEs and AESIs will be followed-up by the investigator until satisfactory resolution. Annually all SARs will be reported as the DSUR to the competent authorities and the leading ethics committee, including all SUSARs.

Withdrawal from further treatment shall be at the discretion of the investigator.

17.8 **SUSAR Reporting**

Expected serious adverse reactions are listed in the Investigator Brochure (IB). All serious unexpected adverse events judged by either the investigator or the GBG Forschungs GmbH as the sponsor will be reported in accordance with applicable local regulations.

18. ADMINISTRATIVE EXECUTION

18.1 **Monitoring**

On-site visits will be made before the study begins and at regular intervals during the study. Other forms of communication (e.g. by telephone, mail, fax etc.) may be used as needed to supplement visits.

The monitor has the responsibility of reviewing the ongoing study with the investigator to verify adherence to the protocol and to deal with any problems if and when they arise.

Special items monitored are: patient enrollment, completeness, exactness and plausibility of data entered on the CRFs, verification against source data and occurrence of Adverse Events. At all times, the confidentiality of study documents is maintained. Monitoring is performed by GBG Forschungs GmbH or designee.

It is the responsibility of the investigator to ensure that, the dispensing and return/destruction of study medication on the drug accountability forms provided is documented correctly. The investigator should ensure that the investigational product use is documented in such a way as to ensure correct dosage. This documentation should confirm that each subject did receive the product dispensed for her and state the identity, including the dosage, of the product received. Drug reconciliation will be verified by a second responsible person at the close-out visit to the site by the study monitor. All discrepancies are accounted for and documented.

The investigator agrees to allow the monitor access to all study materials needed for the monitor to properly review the study progress. The investigator (or deputy) agrees to assist the monitor in resolving any problem that may be detected during the monitoring visit.

18.2 **Sponsor's Responsibilities**

The GBG Forschungs GmbH as the sponsor

- agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the agreed protocol.
- reserves the right to request the withdrawal of a patient due to protocol violations, administrative or other reasons.
- reserves the right to terminate the study prematurely due to persistent protocol violations, administrative or other reasons. Should this be necessary, the procedures will be arranged after review and after consultation by both parties to ensure protection of the patients' interests.

18.3 **Investigator's Responsibilities**

The investigator agrees to conduct the study in accordance with the procedures and requirements laid out in this protocol. In particular, the investigator agrees to conduct the study in accordance with strict ethical principles. Any modification to the agreed protocol must be approved in writing by both GBG Forschungs GmbH as the sponsor and, if appropriate, the ethics committee(s) approving the original protocol before any modifications are put into effect.

On receipt of study medication, the investigator (or deputy) will conduct an inventory of the supplies and complete a supplies receipt. The investigator will retain a copy of this receipt at the site and return the original receipt to the study monitor.

It is the responsibility of the investigator to ensure completeness of the CRFs for each patient in the study, and when a patient completes the study, the investigator must (electronically) sign the complete CRFs for each patient. The investigator must comment on any missing, unused or spurious data on the appropriate CRF.

In addition to the CRFs, the investigator will maintain adequate records that fully document the progress of the study. The investigator has to state that the patient has taken part in a study and record the study number in the patient's medical records. The exact dates of the beginning and the end of treatment should be given as well.

Copies of these study records (and all study-related documents) shall be kept by the investigator for will 10 years after commercialization and till 2 years if development is

halted. All documentation and materials provided by GBG Forschungs GmbH for this study are to be retained in a secure place and treated as confidential material.

The investigator has the right to request termination of the study for administrative or other reasons. Should this be necessary and agreed upon, the procedures will be arranged after review and after consultation by both parties, to ensure protection of the patients' interests.

By signing this document the investigator indicates that he/she has read the protocol, fully understands the requirements and agrees to abide by all protocol requirements.

Further obligations of the investigator are agreed on in the investigator's contract with the GBG Forschungs GmbH as the sponsor.

18.4 **Patient Informed Consent**

Prior to the beginning of specific protocol procedures, the patient is informed about the nature of the study drug and is given pertinent information as to the intended purpose, possible benefits, and possible adverse experiences. The procedures and possible hazards to which the patient will be exposed are explained. Patient insurance for the compensation of patients for possible study-related injury is provided by the GBG Forschungs GmbH as the sponsor according to local law.

An approved informed consent statement will then be read and signed by the patient, and, if required, a witness, and the investigator. The patient will be provided with a copy of the signed informed consent statement. The patient may withdraw from the study at any time without prejudicing future medical treatment. Verification of a signed informed consent statement will be noted on the patient's study Case Report Form.

Patients are informed that pseudonymised data from their case may be stored electronically and that such data will not be revealed to any unauthorised third party. Data will be reviewed by the monitor, an independent auditor and possibly by representatives of regulatory authorities and/or ethics committees. The terms of the local data protection legislation will be applied as appropriate.

18.5 **Confidential Follow-up**

The investigator will be responsible for retaining sufficient information about each patient (e.g. informed consent form, name, address, phone number, and identity in the study) so that regulatory agencies or the GBG Forschungs GmbH as the sponsor may access this information should the need to do so arise. These records should be retained in a confidential manner for as long as legally mandated according to local requirements.

18.6 **Ethics and Regulatory Considerations**

The study described in this protocol is conducted in compliance with the ICH guideline for Good Clinical Practice and applicable regulations in all aspects of preparation, monitoring, reporting, auditing, and archiving.

The final approved protocol and the informed consent statement is reviewed by a properly constituted Ethics Committee (EC) / Institutional Review Board (IRB). The EC/IRB decision concerning the conduct of the study is made in writing to the investigator.

The investigator or designee agrees to make required progress reports to the EC/IRB, as well as report any serious adverse reaction (SAR) and suspected unexpected serious adverse reaction (SUSAR). The investigator or designee also informs the EC/IRB of reports of serious adverse reactions (provided to him/her by the GBG Forschungs GmbH) in other clinical studies conducted with the study drug if deemed necessary by the GBG Forschungs GmbH as the sponsor.
The EC/IRB must be informed by the sponsor of the termination of the study.

The sponsor is responsible for notifying the regulatory authorities of the study.

18.7 **Declaration of Helsinki**

This study is to be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice (Sommerset West, 1996), (Appendix 10).

Modification of the Protocol

Any modifications to the protocol which may impact on the conduct of the study, on the potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects, will require a formal amendment to the protocol. Such an amendment will be agreed upon by the Protocol Board, and approved by the EC/IRB prior to implementation, and reported to the health authorities in accordance with local regulations.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by the Protocol Board and will be documented in a memorandum. The EC/IRB may be notified of administrative changes at the discretion of the investigator.

18.8 **Study Documents**

All information concerning the study drug and trial conduction, such as scientific data and material not previously published are considered confidential and shall remain the sole property of GBG Forschungs GmbH.

The investigator agrees to use the information provided for the conduct of this study only and to use it for no other purposes unless she/he obtains the written consent of the GBG Forschungs GmbH as the sponsor.

18.9 **Case Report Forms**

All key study information must be recorded in the patient's hospital notes. Study procedures will be fully online documented on the electronic CRFs provided through the GBG own EDC-System (electronic data capture) MedCODES. The investigator will be prompted with an interface to enter his/her login data to sign the document electronically according to the FDA regulatory known as "21 CFR Part 11".

The CRFs, as well as the protocol, are confidential. The CRFs remain the property of the GBG Forschungs GmbH at all times. On the CRFs, patients should be identified by their patient number.

Patients' data entries may only be made by the persons registered on the form "Delegation of responsibilities and signature list of investigators and medical staff".

For details concerning the CRF submission process, please refer to the application manual and electronic training material.

18.10 **GCP Documents**

The following documents are collected from the investigator's site:

Signed Investigator's Agreement,

Curricula vitae of all investigators and medical staff,

Name and address of the laboratories,

List of laboratory reference ranges and a quality certificate,

Form "Delegation of responsibilities and signature list of investigators and medical staff",

Any other relevant GCP documents.

18.11 **Archiving**

After completing the study, the GBG Forschungs GmbH will retain all study documents for at least ten years after the completion of the study.

The investigator shall arrange for the retention of the patient identification codes, patient files and other source data until at least ten years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least two years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to

be retained for a longer period of time if required by the competent authorities or by agreement with the GBG Forschungs GmbH as the sponsor.

Patient files and other source data shall be kept for the maximum period of time permitted by the hospital, institution or private practice.

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or their representatives. Essential documents must be retained for 10 years after commercialization and till 2 years if development of palbociclib is halted.. The investigator will appoint individuals responsible for the storage of essential documents and access to the documents will be restricted to those people. Any alterations to essential documents must be traceable. The investigator must contact the sponsor before destroying any study-related documentation.

18.12 **Use of Information and Publication**

To allow for the use of the information derived from this clinical study and to ensure compliance to current regulations, the investigator is obliged to provide the sponsor with complete test results and all data obtained in this study. This information is only made available to physicians and to the competent authorities, unless the sponsor is under legal obligation to pass it on a third party. The final statistical trial report will be prepared by the responsible biostatistician and the final medical report by the coordinating investigator and the sponsor.

A publication policy will describe the process of preparation of any publication as well as the selection of authors. No publication is allowed by individual investigators without approval by the ICS.

The data are owned by GBG. However, GBG are only allowed to use these for any purposes after approval by International Principal Investigator.

18.13 **Finance and Insurance**

Details on finance and insurance will be outlined in a separate agreement between the investigator and the sponsor.

19. SUBSTUDIES

19.1 **TBD**

20. INVESTIGATOR'S AGREEMENT

I have read the protocol

Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy

"PENELOPE^{B}"

GBG-78 - BIG 1-13

EudraCT No.: 2013-001040-62

FDA IND: 123239

Protocol G (Version 11 - 9th April 2019)

and agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name **(CAPITAL LETTERS)**

_____ _____

Principal Investigator's Signature Date

_____

GBG Principal Investigators Site Number

21. APPENDICES

21.1 Appendix 1: CPS-EG Score / AJCC Breast Cancer Staging

Point Assignments for the CPS + EG Staging System

Stage	Points
Clinical stage	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
Pathologic stage	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2
Tumor marker	
ER negative	1
Nuclear grade 3	1

Abbreviations: CPS + EG, clinical-pathologic staging system incorporating ER-negative disease and nuclear grade 3 tumor pathology; ER, estrogen receptor.

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0

* T1 includes T1mi.

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

21.2 Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

21.3 Appendix 3: List of foods and drugs known to be CYP3A4 inhibitors or inducers:

The concurrent use of CYP3A inhibitors, including amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit, are not allowed in the study. The concurrent use of CYP3A inducers, including carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort, are not allowed in the study.

Please refer additionally to P450 Drug Interaction Table from Indiana University department of medicine:

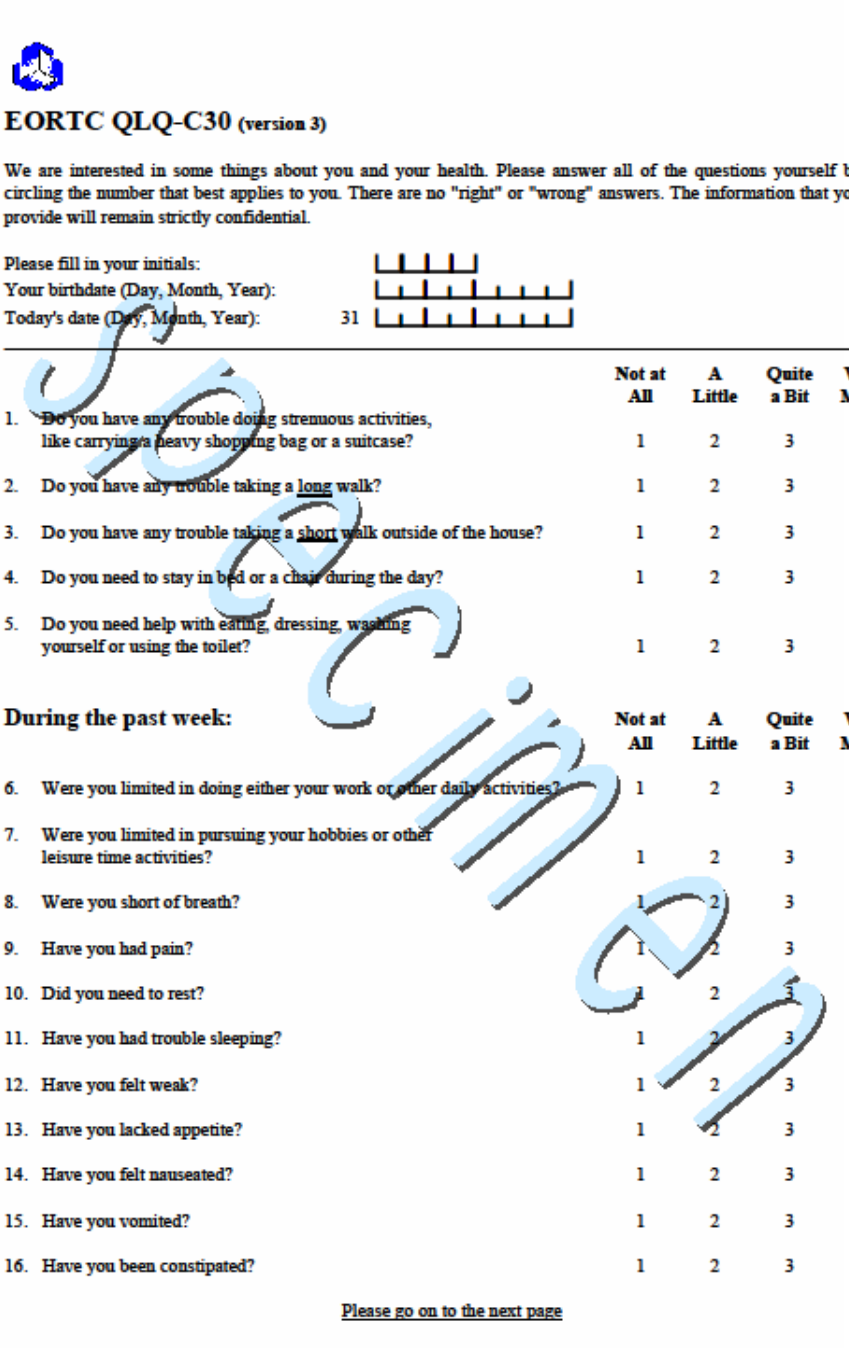
http://medicine.iupui.edu/clinpharm/ddis/main-table

21.4 **Appendix 4: List with examples of Drugs Known to Predispose to Torsade de Pointes**

No longer applicable.

21.5 Appendix 5a and Appendix5b:EORTC OLQ-30 to be used in combination with Cancer Related Fatigue: EORTC QLQ-FA13

http://groups.eortc.be/qol/eortc-qlq-c30



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Cancer Related Fatigue: EORTC QLQ-FA13 will be used http://groups.eortc.be/qol/cancer-related-fatigue-eortc-qlq-fa13

21.6 Appendix 6 EORTC QLQ BR-23

http://groups.eortc.be/qol/eortc-modules

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

21.7 **Appendix 7 GAD7**

http://www.phqscreeners.com/overview.aspx

Over the last 2 weeks, how often have you been bothered by the following problems? (Use "✔" to indicate your answer")	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
(For office coding: Total Score T	_____	= _____	+ _____	+ _____)

21.8 **Appendix 8 EQ5D**

http://www.euroqol.org/

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

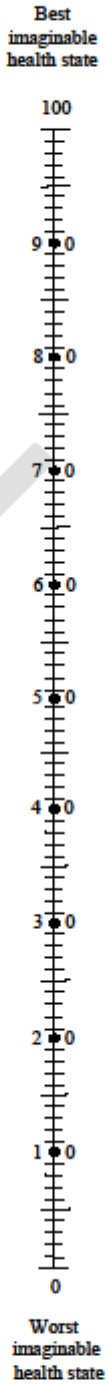
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



21.9 Appendix 9: RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from [123]*E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247*

Categorizing Lesions at Baseline

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).

Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.

Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.

Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Objective response status at each evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.

Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

Indeterminate. Progression has not been documented, and

one or more target measurable lesions have not been assessed,

or assessment methods used were inconsistent with those used at baseline,

or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure),

or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

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

Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 1. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

21.10 Appendix 10: Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

http://www.wma.net/en/30publications/10policies/b3/index.html

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53th WMA General Assembly, Washington 2002

55th WMA General Assembly, Tokyo 2004

59th WMA General Assembly, Seoul, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

21.11 Appendix 11: National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE version 4.0

- Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
- When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
- The evaluator must attempt to discriminate between disease / treatment and related signs / symptoms.
- An accurate baseline prior to therapy is essential.

Please use the pdf from the following website:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

21.12 Appendix 12: Assessment of response to neoadjuvant chemotherapy

Definition of response by physical examination and imaging tests

Clinical (c) and imaging (i) response will be assessed by physical examination and imaging tests. Sonography or MRI are the preferred examination, however, if sonography appears not to provide valid results or is not performed; other imaging tests will be considered with the following priority: MRI, mammography, computed tomogram. The same imaging method should be considered for the measurement before and after treatment.

- Clinical complete response (cCR) – (iCR)

Complete disappearance of all tumor signs in the breast as assessed by imaging test. The response of the axillary nodes is not to be considered.

- Clinical partial response (cPR) – (iPR)

Reduction in the product of the two largest perpendicular diameters of the primary tumor size by 50% or more assessed by palpation or imaging test. In patients with multifocal or multicentric disease, the lesion with the largest diameters should be chosen for follow-up. The response of the axillary nodes is not to be considered.

- Clinical stable disease (cNC) – (iNC)

No significant change in tumor size during treatment. This category includes no change, an estimated reduction of the tumor area by less than 50%, or an estimated increase in the size of the tumor area lesions of less than 25% measured by palpation or imaging test.

- Clinical progressive disease (cPD)

Development of new, previously undetected lesions, or an estimated increase in the size of pre-existing lesions by 25% or more after at least two cycles of therapy.

For all these defined categories of efficacy, the proportion of patients with success will be determined and appropriate confidence intervals will be calculated.

Patients in whom success cannot be determined (e.g. patients in whom histology is not evaluable) will be included in the denominator, i.e. these patients will affect the success rate in the same way as treatment failures. The clinical tumor response by palpation prior to surgery will also be presented, if applicable

21.13 **Appendix 13 Administrative Letter 1**

Study Title: **Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Linase (CDK) 4/6 inhibitor in patients with hormon-receptor-positive, Her2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy „PENELOPE_B"**
Study Code: **GBG-78, BIG 1-13, NSABP-B-54-I**
EudraCt No: **2013-001040-62**

Dear Investigators,
the following summary is provided in regard to the nonclinical data:

Palbociclib has been evaluated in safety pharmacology, genetic toxicity, reproductive and development (fertility and early embryonic development, embryofetal development), and repeat-dose toxicity studies of up to 15-weeks duration in the rat and dog. Based on the nonclinical safety studies conducted with palbociclib, the primary palbociclib-related systemic toxicities were observed in hematolymphopoietic tissues (decreased cellularity, increased iron pigment, decreases in peripheral leukocytes and RBC parameters) and male reproductive organs (degeneration of seminiferous tubules, secondary epididymal hypospermia and increased intratubular cellular debris). Partial to complete reversibility of toxicities was demonstrated following a 4 week recovery period, with the exception of the male reproductive organ findings in the dog. These toxicities occurred in both rats and dogs, and are consistent with the intended pharmacologic effect of palbociclib (i.e., cell cycle inhibition) (Fink et al, 2001; Arguello et al, 1998; Bartkova et al, 2003). Palbociclib was also identified with the potential to cause QT prolongation (Section 6.3.4 Penelope Protocol), developmental effects, and aneugenicity. Developmental effects that were considered adverse included a decrease in fetal body weights in rats and a low incidence of small phalanges on the forepaws in rabbits. A no effect level for aneugenicity was observed at approximately 7-fold higher than unbound systemic AUC_{24} exposures associated with the human clinical dose of 125 mg QD.

Palbociclib is being further evaluated for chronic toxicity in a 6-month rat and 9-month dog repeat-dose toxicity study.

Gunter von Minckwitz, MD Principal Investigator — Jan 14th 2014 Date

Notice for sites: Please file this administrative letter in the protocol section

21.14 **Appendix 14 Administrative Letter 2**

Study Title: **Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormon-receptor-positive, Her2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy „PENELOPE_B"**
Study Code: **GBG-78, BIG 1-13, NSABP-B-54-I**
EudraCT No: **2013-001040-62**

Dear Investigators,
the following summary is provided in regard to the administration of Palbociclib:

Preliminary results from recently performed food effect study from Pfizer, A5481021, a Phase 1, open-label 4 sequence 4 period crossover study of palbociclib (PD-0332991) in healthy volunteers to estimate the effect of food on the bioavailability of palbociclib, suggest that the administration of palbociclib with food results in more consistent drug uptake and exposure than administration of palbociclib in a fasted state. The patients in this study are administered the Phase III Yellow/Caramel formulation which is or will be supplied for your study.

Because of these findings, we request that patients be instructed to take palbociclib with food. This may begin immediately. The dosing instructions for PD-0332991/placebo will be updated in the next Protocol Amendment to read, "Patients should take PD-0332991/placebo with food."

This change does not significantly affect the study's scope, safety, or scientific quality.

Gunter von Minckwitz, MD Principal Investigator — January 15 2014 Date

Notice for sites: Please file this administrative letter in the protocol section

21.15 **Appendix 15 Administrative Letter 3**

Study Title: **Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Linase (CDK) 4/6 Inhibitor in patients with hormon-receptor-positive, Her2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy „PENELOPE_B"**
Study Code: **GBG-78, BIG 1-13, NSABP-B-54-I**
EudraCt No: **2013-001040-62**

Dear Investigators,

In Administrative Letter 1 we informed you, that Palbociclib is being further evaluated for chronic toxicity in a 6-month rat and 9-month dog repeat-dose toxicity study.
Following Data were released by Pfizer on 27th Jan 2014 as Special Safety Concern Report:
The study entitled "27-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with PD-0332991 in Rats with a 12-Week Recovery Phase (Study 8282224; Sponsor Reference Number 13LJ036)
The identification of cataracts in rats following 27-weeks of intermittent dosing represents a new target organ toxicity. In the previous rat and dog repeat-dose toxicity studies up to 15 weeks duration, the primary target organ findings were observed in the hematolymphopoietic and male reproductive tissues.
The minimal dose level for cataract formation has not been identified from the 27-week rat toxicity study, based on the histological data (lens degeneration was noted microscopically).
Cataracts were identified from ophthalmic evaluations at the lower examined dose of 30 mg/kg/day in males but at no dose in females.
While the impact of this nonclinical finding is considered to suggest a potential risk to human subjects, the overall benefit-risk for palbociclib remains favorable.

Secondly Proton Pump inhibitors are not recommended during active treatment with Palbocilib:
Preliminary results from the recently performed antacid effect from Pfizer Sponsored study : A5481018, "a Phase I, open-label fixed-sequence 2-period crossover study of palbociclib in healthy subjects to investigate the potential effect of antacid treatment on the pharmacokinetics of a single oral dose administered under fasted conditions", suggest that the administration of PPIs (such as rabeprazole), when concurrently given with palbociclib may lead to a significant decrease in palbociclib exposure. This study uses the free-base formulation of Palbociclib which is also provided for your study. Final results will be made available to investigators and regulatory bodies once the report is complete
As a result of these findings, we request that patients be instructed to refrain from the use of proton pump inhibitors.
If needed, alternative antacid therapies may be used including H2-receptor antagonists, and locally acting antacids. H2-receptor antagonists should be administered with a staggered dosing regimen (twice daily). The dosing of palbociclib should occur at least 10 hours after H2-receptor antagonist evening dose and 2 hours before the H2-receptor antagonist morning dose. Local antacid should be given at least 2 hours before or after palbociclib administration.

Jan 30, 2014
Gunter von Minckwitz, MD Principal Investigator — Date
Notice for sites: Please file this administrative letter in the protocol section

21.16 **Appendix 16 Administrative Letter 4**

Study Title: **Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Linase (CDK) 4/6 Inhibitor in patients with hormon-receptor-positive, Her2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy „PENELOPE_B"**
Study Code: **GBG-78, BIG 1-13, NSABP-B-54-I**
EudraCt No: **2013-001040-62**

Dear Investigators,

After approval by your competent authority Inclusion criterion number 9 changes:

From (Old)

9. Less than 16 weeks interval since the date of final surgery and date of randomization (including the radiotherapy period).

To (New)

9. Less than 16 weeks interval since the date of final surgery or less than 10 weeks from completing radiotherapy (whichever occurs last) and date of randomization.

This is not significantly changing the patient population and the scope of the trial.

07. Mar 2014

Gunter von Minckwitz, MD Principal Investigator — Date

Notice for sites: Please file this administrative letter in the protocol section

21.17 Appendix 17 Administrative Letter 5

Study Title: **Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Linase (CDK) 4/6 Inhibitor in patients with hormon-receptor-positive, Her2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy „PENELOPE_B"**
Study Code: **GBG-78, BIG 1-13, NSABP-B-54-I**
EudraCt No: **2013-001040-62**

Dear Investigators,

In Administrative Letter 3 (30th Jan 2014) we informed you about the identification of cataracts in rats following 27-weeks of intermittent dosing with palbociclib (Safety Concern Notification Pfizer 29th Jan 2014) . This is a follow-up to communicate further data that emerged from this toxicity study showing correlation between altered glucose metabolism and the formation of cataracts/lens degeneration. A special safety concern notification was released by Pfizer on 18th July 2014.

In Administrative Letter 1 we informed you that palbociclib is being further evaluated in dog Toxicity Study (9-month). In dog toxicity studies (15-week and 39-week), no altered glucose levels and no cataracts/lens degeneration have been observed (lack of lens degeneration not yet confirmed in the 39-week study; histopathology pending).

Hyperglycemia and diabetes mellitus are currently not considered to be identified clinical risks and are not considered to be adverse drug reactions (ADRs) of palbociclib.

According to exclusion Criterion #10 a severe acute or chronic medical condition that may increase the risk associated with study participation needs to be excluded, which includes uncontrolled diabetes mellitus.

Before a patient enters the Penelope study please ensure their diabetes is easily controlled medically.
As an amendment to the protocol we ask you to measure HbA1C-levels with the following visits:
Baseline,
Day1 Cycle 3 (9th week +/- 7days),
Day1 Cycle 7 (25th week +/- 7days)
Day1 Cycle 11 (41st week +/- 7days)
End of Therapy (within 30 days after the last dose).
These measurements can be done at a local laboratory convenient for the patient. In case of a signal please refer the patient to a diabetologist or a diabetes advisor to easily control the diabetes and enter the concomitant medication in the CRF.

Gunter von Minckwitz, MD Principal Investigator — July 21st 2014 Date

Notice for sites: Please file this administrative letter in the protocol section

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