A Study of Palbociclib in Addition to Standard Endocrine Treatment in Hormone Receptor Positive Her2 Normal Patients With Residual Disease After Neoadjuvant Chemotherapy and Surgery (PENELOPE-B)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2013 by German Breast Group

Sponsor:
German Breast Group

Collaborator:
Pfizer

Information provided by (Responsible Party):
German Breast Group

ClinicalTrials.gov Identifier:
NCT01864746

First received: May 14, 2013
Last updated: November 18, 2013
Last verified: November 2013
History of Changes

Purpose

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 2453 patients with HR-positive/HER2-normal tumors from the German neoadjuvant studies' meta-database. 24% of these patients had a score of 3 or higher and showed a 3-years DFS of 74% 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.

The PENELOPEB 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.

Condition	Intervention	Phase
Luminal A Breast Cancer Luminal B Breast Cancer CPS-EG Score Postneoadjuvant Treatment With CDK 4/6 Inhibitor Hormonreceptor Positive	Drug: Palbociclib PD-0332991 Behavioral: Patient reported outcomes Drug: Placebo	Phase 3

Study Type: Interventional

Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official 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"

Resource links provided by NLM:

Genetics Home Reference related topics: breast cancer

MedlinePlus related topics: Breast Cancer Cancer Hormones

Drug Information available for: Palbociclib

U.S. FDA Resources

Further study details as provided by German Breast Group:

Primary Outcome Measures:

- Invasive disease free survival (iDFS) for palbociclib vs. placebo in patients with high CPS-EG score after neoadjuvant chemotherapy receiving standard adjuvant endocrine therapy for HR-positive/HER2-normal primary breast cancer. [Time Frame: Time-to-Event Outcome measure. Final analysis on the primary endpoint and secondary efficacy endpoints (except for OS) Analysis will be conducted when 233 events observed. Assessed up to 71 months till approx. Dec 2019.] [Designated as safety issue: Yes]

  Invasive disease-free survival (iDFS) is defined according to Hudis (J Clin Oncol 2007) 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)). Two interim efficacy analyses will be performed in the study. First interim analysis: Safety, early stopping Second interim analysis: Safety, early stopping, sample size adjustment

Secondary Outcome Measures:

- iDFS excluding second non-breast cancers [Time Frame: Time-to-Event Outcome Measure up to 71 months]
  [Designated as safety issue: Yes]

Invasive disease-free survival (iDFS) is defined according to Hudis (J Clin Oncol 2007) as the time period betw een randomization and first event.

- distant disease free survival (DDFS) [Time Frame: Time-to-Event Outcome Measure up to 71 months] [Designated as safety issue: Yes]

  Distant disease free survival (DDFS) is defined as the time period betw een randomization and diagnosis of first distant breast cancer recurrences.

- overall survival (OS) [Time Frame: Time-to-Event Outcome Measure up to 71 months - and post study] [Designated as safety issue: No]

  Overall survival (OS) is defined as the time period betw een randomization and death of any cause. An interim OS analysis w ill be conducted at the time of final iDFS analysis and final OS analysis w ill be conducted at a later time. In addition Relapse and Mortality data w ill be collected post study.

- iDFS per treatment group in patients w ith luminal-B tumors (as determined by e.g. PAM50 or any other commercially available test at the time of analysis) [Time Frame: Time-to-Event Outcome Measure up to 71 months] [Designated as safety issue: No]

  see above for event definition

- compliance and safety according to NCI-CTCAE Version 4.0 [Time Frame: 2019 and w ith interim analysis on safety] [Designated as safety issue: Yes]

  Descriptive statistics for the 2 treatments w ill be given on the number of patients w hose treatment had to be reduced, delayed or permanently stopped.

- patients reported outcomes EORTC QLQ C30, • EORTC QLQ BR-23, • EORTC QLQ FA-13 Fatigue, • GAD7 patient self-rating mood scale [Time Frame: Change Outcome up to 71 months] [Designated as safety issue: No]

  Screening, Cycle 1, 3, 5, 7, 9, 11, End of treatment and thereafter every 6 months until 233 events are observed

- quality-adjusted life years (QALY), health economic outcomes EQ-5D [Time Frame: Change Outcome Measure up to 71 months] [Designated as safety issue: No]

  Screening, Cycle 1, 3, 5, 7, 9, 11, End of treatment and thereafter every 6 months

- Area under the Curve (AUC), Cmax [Time Frame: pre-dose, 2, 4, 6, 8, and 24 hours] [Designated as safety issue: No]

  Drug-drug interactions (DDI) potential for palbociclib - endocrine combination therapy In the first 24 patients receiving tamoxifen or anastrozol together w ith palbociclib/placebo plasma PK samples w ill be draw n on pre-dose and 2, 4, 6, 8, and 24 hours post-dose for DDI assessment. In the first 24 patients receiving gosereline and tamoxifen together w ith palbociclib/placebo, plasma PK samples w ill be draw n on Cycle 2 and Cycle 3 Days 1 and Day 14 pre-dose for DDI assessment. In addition in the first 24 patients receiving gosereline and tamoxifen together w ith palbociclib/placebo, plasma PK samples w ill be draw n on Cycle 2 and Cycle 3 Days 1 and Day 14 pre-dose for DDI assessment.

- correlations betw een exposure and efficacy and/or safety findings [Time Frame: Pharmacokinetic Outcomes Measure mit Cmax and AUC] [Designated as safety issue: No]

  Trough concentrations of PD-0332991 w ill be collected pre-dose on Day 14 of cycle 1 and 2 for all patients (including letrozol taking patients).

Other Outcome Measures:

- Scores and markers for their prognostic value in this specific trial setting and their predictive information on the efficacy and/or safety of palbociclib [Time Frame: pre and posttherapy up to 13months] [Designated as safety issue: No]

Estimated Enrollment:	800
Study Start Date:	November 2013
Estimated Study Completion Date:	November 2021
Estimated Primary Completion Date:	December 2019 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Active Comparator: Palbociclib Palbociclib at a dose of 125 mg once daily, day 1 to day 21 follow ed by 7 days off treatment in a 28-day cycle for thirteen cycles	Drug: Palbociclib PD-0332991 Endocrine treatment as background therapy usually starts prior to study entry Behavioral: Patient reported outcomes

Placebo Comparator: Placebo Placebo of palbociclib once daily day 1 to day 21 followed by 7 days off treatment in a28-day cycle for thirteen cycles	Behavioral: Patient reported outcomes Drug: Placebo

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Female
Accepts Healthy Volunteers: No

Criteria

Inclusion 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.
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% 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 of the breast, or if not possible, of residual nodal invasion. In case of bilateral breast cancer status has to be 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.
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 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 (including the radiotherapy period).
10. Completion of adjuvant radiotherapy. Radiotherapy is indicated to the breast in all patients treated with breast conserving surgery and to chest wall in all patients with cT3/cT4, R1 or ypN+ disease treated by mastectomy.
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 calculated using local estrogen receptor status and grade assessed on core biopsies taken before start of neoadjuvant treatment
13. Age at diagnosis at least 18 years.
14. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.
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 < 2,000/mm³ (< 2.0 x 109/L); Platelets <100,000/mm³ (< 100 x 109/L); AST and/or ALT > 1.5 x upper normal limits (UNL); alkaline phosphatase > 2.5 x UNL, total serum bilirubin > 1.25 x UNL; 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. Current severe or uncontrolled systemic disease
4. Evidence for infection including wound infections, HIV, Hepatitis
5. QTc >480 msec or a family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation,

or Torsade de Pointes (TdP).

6. Uncontrolled electrolyte disorders that can compound the effects of a QTc prolonging drug (eg, hypocalcemia, hypokalemia, hypo-magnesemia).
7. 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.
8. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.
9. 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.
10. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
11. Recent (within the past year) or active suicidal behavior.
12. Pregnancy or lactation period. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures (barrier methods, intrauterine contraceptive devices, sterilization) during study treatment. A serum pregnancy test must be negative in premenopausal women or women with amenorrhea of less than 12 months.
13. Major surgery within 2 weeks prior to randomization.
14. Prior neoadjuvant endocrine treatment. Adjuvant endocrine treatment can be started anytime post-surgery.
15. Prior treatment with any CDK4/6 inhibitor.
16. Patients treated within the last 7 days prior to randomization with drugs known to be CYP3A4 inhibitors or inducers or drugs that are known to prolong the QT interval.
17. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry.
18. Male patients.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT01864746

Contacts

Contact: Ioannis Gkantiragas, PhD +49 6102 7480 ext 337 penelope@germanbreastgroup.de

Contact: Heike Beckel, PhD +49 6102 7480 ext 240 penelope@germanbreastgroup.de

Locations

Germany

Luisenkrankenhaus **Recruiting**
Duesseldorf, Germany, 40235

Sponsors and Collaborators

German Breast Group

Pfizer

Investigators

Principal Investigator: Gunter von Minckwitz, MD, Prof ASCO, AACR, ESMO, DKG, DGGG, AGO, DGS, BIG, BCIRG, St. Gallen Consensus Panel

More Information

Additional Information:

Related Info EXIT

Publications:

Mittendorf EA, Jeruss JS, Tucker SL, Kolli A, Newman LA, Gonzalez-Angulo AM, Buchholz TA, Sahin AA, Cormier JN, Buzdar AU, Hortobagyi GN, Hunt KK. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol. 2011 May 20;29(15):1956-62. doi: 10.1200/JCO.2010.31.8469. Epub 2011 Apr 11.

Musgrove EA, Caldon CE, Barraclough J, Stone A, Sutherland RL. Cyclin D as a therapeutic target in cancer. Nat Rev Cancer. 2011 Jul 7;11(8):558-72. doi: 10.1038/nrc3090. Review.

ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature. 2012 Sep 6;489(7414):57-74. doi: 10.1038/nature11247.

Finn RS, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ, Ginther C, Atefi M, Chen I, Fowst C, Los G, Slamon DJ. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res. 2009;11(5):R77. doi: 10.1186/bcr2419.

Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, Assad L, Poniecka A, Hennessy B, Green M, Buzdar AU, Singletary SE, Hortobagyi GN, Pusztai L. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol. 2007 Oct 1;25(28):4414-22. Epub 2007 Sep 4.

Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst. 2005 Feb 2;97(3):188-94.

von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Konecny GE, Denkert C, Nekljudova V, Mehta K, Loibl S. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012 May 20;30(15):1796-804. doi: 10.1200/JCO.2011.38.8595. Epub 2012 Apr 16.

Responsible Party:	German Breast Group
ClinicalTrials.gov Identifier:	NCT01864746 History of Changes
Other Study ID Numbers:	GBG78/BIG 1-13/NSABP-B-54-I, 2013-001040-62
Study First Received:	May 14, 2013
Last Updated:	November 18, 2013
Health Authority:	United States: Food and Drug Administration Austria: Agency for Health and Food Safety Brazil: Ministry of Health Canada: Public Health Agency of Canada France: Agence Nationale de Sécurité du Médicament et des produits de santé Germany: Federal Institute for Drugs and Medical Devices Italy: The Italian Medicines Agency Japan: Pharmaceuticals and Medical Devices Agency Korea: Food and Drug Administration Spain: Agencia Española de Medicamentos y Productos Sanitarios United Kingdom: Medicines and Healthcare Products Regulatory Agency

Additional relevant MeSH terms:
Breast Neoplasms
Breast Diseases
Neoplasms
Neoplasms by Site
Skin Diseases

ClinicalTrials.gov processed this record on April 13, 2015