Endocrine adjuvant therapy may have started before randomization and be ongoing at that time.

Approximately 4600 patients from approximately 500 global sites will be randomized into one of the two treatment arms with a 1:1 randomization ratio. The dosing schedule for both Arms, and potential dose reduction strategies, are given in section 9):

**Arm A**: palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21, followed by 7 days off treatment in a 28-day cycle for a total duration of 2 years (refer to 6.1.2 for details), in addition to standard adjuvant endocrine therapy for a duration of at least 5 years.

**Arm B**: standard adjuvant endocrine therapy for a duration of at least 5 years

Standard endocrine therapy (also referred to as background treatment) can be tamoxifen or aromatase inhibitor with or without LHRH agonist.

In order to participate in the trial, a patient must fulfill all inclusion criteria and must not meet any of the exclusion criteria. Furthermore, a patient will need to consent for study participation and to the collection storage and analysis of his/her blood and tumor tissue samples for biomarker research as specified in section 14. Prior to randomization, a representative tumor tissue block must be made available to the central sample repository.

**Figure 1: PALLAS Study Schema**

<table>
<thead>
<tr>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>• N = 4600</td>
</tr>
<tr>
<td>• Inclusion Criteria:</td>
</tr>
<tr>
<td>~ HER2+ and HER2-</td>
</tr>
<tr>
<td>~ Stage II or III (IIA limited to 1000 patients)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm A Palbociclib (2 yrs) + Endocrine Treatment (5+ yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival/Disease Follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm B Endocrine treatment (5+ yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRO &amp; Adherence Monitoring</td>
</tr>
</tbody>
</table>

| FFPE Tissue sample received at central biorepository |

<table>
<thead>
<tr>
<th>Stratification Factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anatomic stage (IIA vs IB/III), assessed by pathologic staging or by clinical staging if pre-operative therapy was given with the higher stage determining eligibility</td>
</tr>
<tr>
<td>• Neo/adjuvant chemotherapy (yes vs no)</td>
</tr>
<tr>
<td>• Age (&lt; 50 vs &gt; 50 years)</td>
</tr>
<tr>
<td>• Geographic region (North America vs Europe vs Other)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neo/Adjuvant systemic therapy</td>
<td></td>
</tr>
</tbody>
</table>

**Participating Groups and Academic Identifiers:**
AFT (AFT-05), ABCSG (ABCSG 42), BIG (BIG 14-03), PrECOG (PrE0109), NSABP (B-57-1)
4. Patient Selection

4.1. Inclusion Criteria

Please note that waivers to eligibility requirements are not allowed.

**Patients must meet the following criteria for study entry:**

4.1.1. Patient/Disease Specifics

1. Signed informed consent obtained prior to any study specific assessments and procedures.
2. Age ≥18 years (or per national guidelines).
3. Premenopausal and postmenopausal women or men with Stage II (Stage IIA limited to a maximum of 1000 patients) or Stage III early invasive breast cancer per AJCC (American Joint Committee on Cancer) Breast Cancer Staging version 7 / UICC (Union for International Cancer Control). Baseline staging to document absence of metastatic disease is not required, however is recommended as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms). If performed, reports of these examinations must be available. Examination type for staging, i.e. X-ray, sonography, bone scan, CT, MRI, and/or PET-CT, is at the discretion of the investigator.

   If neoadjuvant systemic therapy was received (either chemotherapy or endocrine therapy), either initial clinical stage (determined by physical and/or radiologic examination) or post-operative pathologic stage can be used for eligibility purposes, with the higher stage determining eligibility.

4. Patients with multicentric and/or multifocal and/or bilateral early invasive breast cancer whose histopathologically examined tumors all meet pathologic criteria for ER+ and/or PR+ and HER2-.

5. Patients must have histologically confirmed hormone receptor positive (ER+ and/or PR+), HER2-, early invasive breast cancer. ER, PR and HER2 measurements should be performed according to institutional guidelines, in a CLIA-approved setting in the US or certified laboratories for Non-US regions. Cut-off values for positive/negative staining should be in accordance with current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines. Patients with equivocal HER2 in situ hybridization results according to current ASCO/CAP guidelines are eligible, as long as they have not received and are not scheduled to receive anti-HER2 treatment. Testing may occur on diagnostic core or surgical tumor tissue.

6. Patients must have undergone breast surgery for the current malignancy.

7. A formalin-fixed paraffin-embedded (FFPE) tumor tissue block must be transmitted to a central sample repository and confirmation of receipt must be available prior to randomization. For details please refer to section 8.2.

8. ECOG performance status 0-1.

9. Patients must be able and willing to swallow and retain oral medication without a condition that would interfere with enteric absorption.

Participating Groups and Academic Identities:
AFT (AFT-05), ABCSG (ABCsG 42), BIG (BIG 14-03), PrECOG (PrE0109), NSABP (B-57-I)
(10) Serum or urine pregnancy test must be negative within 7 days of randomization, in women of childbearing potential. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation. Women of childbearing potential and male patients randomized into treatment Arm A or B must use adequate contraception for the duration of protocol treatment and for 6 months after the last treatment with palbociclib if they are in arm A. Adequate contraception is defined as one highly effective form (i.e. abstinence, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusive cap with spermicidal foam / gel / film / cream / suppository).

4.1.2. Prior Treatment Specifics

(11) Patients may or may not have received neo/adjuvant therapy, but must be after last dose of chemotherapy and/or biologic therapy and must have sufficient resolution of side effects per physician assessment at the time of randomization.

(12) Patients may or may not have received breast/axilla/post-mastectomy chest wall radiotherapy, but must be after last dose of radiotherapy and must have sufficient resolution of side effects per physician assessment at the time of randomization.

(13) Patients must have sufficient resolution of any surgical side effects from the last surgery per physician assessment, with no active wound healing complications at the time of randomization.

(14) Patients must either be initiating or have already started **adjuvant hormonal treatment**. Patients may already have initiated endocrine therapy at the time of randomization, but randomization must take place within 12 months of date of histological diagnosis and within 6 months of initiating standard adjuvant endocrine therapy. Patients who received **neoadjuvant endocrine therapy** are eligible as long as they are enrolled within 12 months of initial histological diagnosis and after completing no more than 6 months of adjuvant endocrine therapy. Patients may be receiving either tamoxifen or aromatase inhibitor (AI: letrozole, anastrozole, or exemestane). For premenopausal patients and men, concurrent LHRH agonist use is allowable and may also be ongoing at the time of randomization.

4.1.3. Baseline Body Function Specifics

(15) Absolute neutrophil count ≥ 1,500/mm³.
(16) Platelets ≥ 100,000/mm³.
(17) Hemoglobin ≥ 10g/dL.
(18) Total serum bilirubin ≤ ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert’s Syndrome.
(19) Aspartate amino transferase (AST or SGOT) and alanine amino transferase (ALT or SGPT) ≤ 1.5 × institutional ULN.
(20) Serum creatinine within normal institutional limits or creatinine clearance ≥ 60 mL/min/1.73 m² for patients with serum creatinine levels above institutional ULN.
4.2. Exclusion Criteria

**Patients who meet any of the following criteria will be excluded from study entry:**

1. Concurrent therapy with other Investigational Products.
2. Prior therapy with any CDK inhibitor.
3. Patients with Stage I or IV breast cancer are not eligible. Baseline staging to document absence of metastatic disease is not required, however is recommended as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms). If performed, reports of these examinations must be available. Examination type for staging, i.e. X-ray, sonography, bone scan, CT, MRI, and/or PET-CT, is at the discretion of the investigator.
4. History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib.
5. Patients receiving any medications or substances that are potent inhibitors or inducers of CYP3A isoenzymes within 7 days of randomization (see Section 9.5.2.1 for list of CYP3A inhibitors and inducers).
6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, or psychiatric illness/social situations that would limit compliance with study requirements. Ability to comply with study requirements is to be assessed by each investigator at the time of screening for study participation.
7. Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to randomization, irrespective of the method of contraception used, are excluded from this study because the effect of palbociclib on a developing fetus is unknown. Breastfeeding must be discontinued prior to study entry.
8. Patients with a history of any malignancy are ineligible except for the following circumstances:
   - Patients with a malignancy history other than invasive breast cancer are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy.
   - Patients with the following cancers are eligible, even if diagnosed and treated within the past 5 years: ductal carcinoma in situ of the breast, cervical cancer in situ, and non-metastatic non-melanomatous skin cancers.
9. Patients are not eligible if they have previously received endocrine therapy within 5 years prior to diagnosis of the current malignancy. This includes use for prophylactic reasons, including treatment of osteoporosis or cancer prevention with tamoxifen, raloxifene or AI. Patients may concurrently receive bisphosphonates or rank ligand inhibitors while on this study if necessary for treatment or prevention of osteopenia or osteoporosis.
10. Patients on combination antiretroviral therapy, i.e. those who are HIV-positive, are ineligible because of the potential for pharmacokinetic interactions or increased immunosuppression with palbociclib.
11. Patients with a clinically significant history of liver disease, including viral or other
known hepatitis, current alcohol abuse, or cirrhosis, etc.

Patients receiving concurrent exogenous hormone therapy (hormone replacement therapy, oral or any other hormonal contraceptives such as hormonal contraceptive coil, etc.) are not eligible but topical vaginal estrogen therapy is allowable.