Phase II Safety Study of Palbociclib in Combination with Letrozole or Fulvestrant in African American Women with Hormone Receptor Positive HER2 Negative Advanced Breast Cancer (PALINA study)

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Protocol No.: Version date:

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and International Conference on Harmonization (ICH) guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date: _____

Name of Site: _____

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STUDY SUMMARY

Table 1. Study summary

Title	Phase II safety study of palbociclib in combination with letrozole or fulvestrant in African American women with hormone receptor positive HER2 negative advanced breast cancer
Protocol Number	2015-1396
Phase	Phase II study
Study Duration	24 months; enrollment over 12 months
Study Center(s)	The study will open at the Georgetown MedStar Cancer Network, University of Chicago and Thomas Jefferson University
Primary Objective	To evaluate the hematological safety of palbociclib with letrozole or fulvestrant in African American women with hormone receptor positive HER2 negative advanced breast cancer. Use of anastrozole or exemestane permitted in the event of letrozole intolerance. Hematological safety is a composite endpoint of episodes of febrile neutropenia and treatment discontinuation due to neutropenia according to current recommendations for management of neutropenia
Secondary Objectives	• To evaluate delays in palbociclib therapy attributed to neutropenia • To evaluate dose reductions in palbociclib therapy attributed to neutropenia • To evaluate grade 3/4 neutropenia • To evaluate the efficacy of palbociclib with letrozole or fulvestrant in African American women with ER/PR positive HER2 negative metastatic breast cancer with evaluable disease. Use of anastrozole or exemestane permitted in the event of letrozole intolerance. • To evaluate correlations between proliferation rates and efficacy • To describe baseline absolute neutrophil count (ANC) prior to cancer diagnosis and the Duffy Null polymorphism (SNP rs2814778 at chromosome 1q23.2) and explore correlations with hematological safety

Important inclusion and exclusion criteria	**Main inclusion criteria:** 1. Self-identified Black, African or African American women of ≥ 18 years of age with proven diagnosis of advanced adenocarcinoma of the breast (locoregionally recurrent or metastatic disease) 2. ER-positive and/or PgR-positive tumor based on local laboratory results 3. HER2-negative breast cancer based on local laboratory results (test to be used as per local practice) 4. Patients must be appropriate candidates for letrozole or fulvestrant therapy. Use of anastrozole or exemestane permitted in the event of letrozole intolerance. 5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 6. Adequate bone marrow function: - Absolute Neutrophil Count (ANC) ≥ 1,000/mm^3 (1.0 x 10^9/L); - Platelets ≥100,000/mm^3 (100 x 10^9/L); - Hemoglobin ≥9 g/dL (90 g/L). **Main exclusion criteria:** 1. Current use of food or drugs known to be potent inhibitors or inducers of CYP3A4 2. Active uncontrolled or symptomatic brain metastases. Previously treated and clinically stable, as per Investigator's judgment, brain metastases are permitted. 3. Previous CDK4/6 inhibitor
Primary endpoint	Proportion of patients who complete planned oncologic therapy without the development of a hematological event defined as episodes of febrile neutropenia and treatment discontinuation due to neutropenia according to current recommendations for management of neutropenia

Secondary endpoint	• Number of patients who required dose delays in palbociclib attributed to neutropenia. • Number of patients who required dose reductions in palbociclib therapy attributed to neutropenia • Rate of grade 3/4 neutropenia • Clinical benefit rate (for those with evaluable disease) at 24 weeks • To evaluate correlations between metabolite and exosomal signature with disease response • To evaluate correlations between baseline ANC prior to cancer diagnosis and the Duffy Null polymorphism (SNP rs2814778 at chromosome 1q23.2) with hematological safety
Correlative studies	Metabolite biomarkers and exosomal signature of endocrine resistance
Oncology study Products, Doses, Routes, Regimens	Palbociclib 125mg once daily taken with food for 21 days followed by 7 days off treatment. For patients enrolled with baseline ANC between 1000 and 1499/uL, initial dose of palbociclib will be 100mg once daily for 21days followed by 7 days off treatment.
Duration of drug administration	Maximum of 12 months.
Statistical Methodology	The study is designed to assess the rate of completion of planned oncology therapy in the absence of a hematological event defined as episodes of febrile neutropenia and treatment discontinuation due to neutropenia. A completion rate of 80% is considered of clinical relevance as to benefit breast cancer patients who are at a higher risk of having ethnic neutropenia where as a completion rate of 60% is considered poor and to justify additional safety studies. A two stage design with a total of 35 patients is used to test if the completion rate is at least 80% versus if it is below 60% with 80% power at a significance level of 5%. An exact confidence interval of the completion rate will be calculated. We estimate there will be no more than a 10% rate of febrile neutropenia. Due to the small sample size, the analysis of secondary endpoints will be descriptive and will not include specific hypothesis testing.

1. INTRODUCTION

1.1. Background

Hormone receptor (HR) positive human epidermal growth factor receptor 2 (HER2) negative breast cancer is the most common subset of breast cancer.[1] Most patients are diagnosed at an early stage and remain relapse-free if treated with a prolonged course of endocrine therapy. However, about one-third of patients with HR positive HER2 negative tumors, diagnosed initially with early stage disease, experience disease recurrence.[2] The fundamental problem is that endocrine agents are only partially effective, typically causing cell cycle arrest and tumor dormancy rather than true cure.

The role of estrogens in BC etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for post-menopausal women with HR positive advanced breast cancer, particularly for those with slowly progressive disease and limited tumor-related symptoms.[3] Studies of estrogen receptor (ER) positive breast cancer cell lines indicate that estrogens[4] and antiestrogens[5] act on sensitive populations of cells in early to mid-G1 phase. G1/S transition is under the control of cyclin-dependent kinases (CDKs) activated by specific complex formation with regulatory cyclins.

Conversion of androgens to estrogens via aromatase enzyme action represents the main source of estrogens in post-menopausal women. Letrozole is an oral nonsteroidal aromatase inhibitor that is approved worldwide for the first line treatment of post-menopausal women with HR positive advanced breast cancer. Letrozole is administered orally in a continuous regimen at a 2.5 mg daily dose. In a multicenter Phase III study in patients with HR positive or HR-unknown advanced breast cancer, letrozole was superior to tamoxifen for time to progression (TTP), time to treatment failure (TTF), overall response rate (ORR), and overall clinical benefit response (CBR).[6] Multiple clinical studies have shown that letrozole is well tolerated.

1.2. Palbociclib

Palbociclib is a novel, first-in-class highly selective oral reversible inhibitor of CDK 4 and 6 that is being studied for use in the treatment of different cancers including breast cancer. The compound inhibits cell proliferation by preventing progression of the cell cycle from G1 into the S phase. In February 3, 2015 the FDA granted accelerated approval to palbociclib (IBRANCE®) in combination with letrozole for first-line therapy of postmenopausal women with locally advanced or metastatic ER-positive HER2-negative breast cancer.

1.2.1. Preclinical Data

Palbociclib inhibits purified CDK4-catalyzed phosphorylation of retinoblastoma protein with an IC50 of less than 20 nM, and also tumor growth of several types of human xenograft tumors (SF-295, MDA-MB-435, Colo-205, and others) grown in mice. Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific retinoblastoma (Rb) phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of Rb.

Palbociclib was tested in vitro on molecularly characterized human BC 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 positive subtype.[7] The combination of palbociclib and aromatase inhibitors has not been tested in preclinical models. However, the combination of palbociclib with tamoxifen has recently been tested in vitro in ER positive human breast cancer cell lines indicating a synergistic interaction[7] and provides a biologic rationale for evaluating the combination of palbociclib with antihormonal therapy in the clinic.

Palbociclib preclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytotoxic activity.

1.2.2. Clinical Activity

Palbociclib was initially evaluated as a single agent in 2 phase I dose escalation trials in patients with advanced malignancies.[8,9] In the first published trial, 33 patients with Rb-positive advanced solid tumors or non-Hodgkin lymphoma refractory to standard treatment received palbociclib once daily for 14 days followed by 7 days off (2 weeks on/1 week off).[8] Overall it was well tolerated with dose-limiting toxicities (DLTs) related primarily to myelosuppresion. There was 1 partial response (PR) and 9 patients had stable disease (SD). The recommended phase II dose (RP2D) was 200mg. In the second study,[9] 41 patients with Rb-positive advanced solid tumors were enrolled, including 5 patients with breast cancer. In this trial, palbociclib was administered on a different dose schedule, with 21 days on followed by 7 days off (3 weeks on/1 week off). Neutropenia was the only dose-limiting effect and the most common nonhematologic grade 3/4 adverse events (AEs) included fatigue, nausea, and abdominal pain. Of the 37 patients evaluable for tumor response, 10 had SD. The RP2D was 125 mg. This study defined the dosage used for subsequent trials.

The results seen in phase I led to a single arm phase II study of palbociclib given as monotherapy in patients with Rb-positive advanced breast cancer.[10] Thirty-seven patients were enrolled and 19% had a CBR, defined as PR and SD for 24 months or longer. Median progression-free-survival (PFS) was 3.7 months overall but was significantly longer for those with HR positive disease compared with HR negative disease (4.5 vs 1.5 months, $P = .03$).

Based on preclinical data demonstrating synergy of palbocliclib with anti-estrogen therapy[7], Finn et al conducted the PALOMA-1 trial.[11] This multicenter, open-label phase II trial enrolled 165 postmenopausal women with ER positive HER2 negative, advanced breast cancer who had not received previous systemic treatment for advanced disease. Patients were randomized in a 1:1 fashion to letrozole 2.5mg daily or letrozole 2.5mg daily plus palbociclib. Median investigator-assessed PFS was 20.2 months (95% CI 13.8-27.5) in the palbociclib plus letrozole arm and 10.2 months (95% CI 5.7-12.6) in the letrozole alone arm (hazard ratio [HR], 0.488, 95% CI 0.319-0.748). In addition, the ORR in patients with measurable disease was higher in the palbociclib plus letrozole compared with the letrozole alone arm (55.4% vs 39.4%).

While the results of the phase II study PALOMA-1 are encouraging, a phase III randomized

double-blind placebo controlled trial was designed to definitely evaluate the role of palbociclib in metastatic breast cancer: PALOMA-2.[12] Eligible patients are postmenopausal women with ER-positive HER2-negative disease who have not received prior therapy for advanced breast cancer, prior CDK 4/6 inhibitors, nor prior (neo)adjuvant treatment with letrozole or anastrozole with a disease free interval less than 12-months from completion of treatment. Patients were assigned to letrozole with palbociclib 125 mg once daily 3 weeks on/1 week off or to letrozole with placebo. This study has completed accrual and results are expected in 2016.

Palbociclib has also been investigated in the second-line setting. In PALOMA-3 study, a phase III randomized (2:1) double blind study, 521 patients with HR-positive, HER2-negative breast cancer that relapsed or progressed on previous endocrine therapy were assigned to fulvestrant with palbociclib or placebo.[13] Premenopausal or perimenopausal women were eligible if also treated with goserelin. Women on the experimental arm had more than double median PFS (primary endpoint) compared with those in the placebo arm (9.2 months vs 3.8 months, HR 0.42, *P* <.001). The relative difference in primary outcome between the placebo and palbociclib groups was consistent regardless of menopausal status of the patients. At the time of this preplanned interim analysis, data on overall survival (secondary endpoint) were immature. Although the efficacy benefit was not as large as seen in the first-line setting, these results have led to an expansion of the currently approved label of palbociclib in breast cancer. In February 2016 the FDA approved the use of palbociclib in combination with fulvestrant in women with HR+ HER2- advanced or metastatic breast cancer after progression on endocrine therapy.

1.2.3. Toxicity

Palbociclib is overall well tolerated, either as monotherapy or in combination with anti-estrogen therapies. However quite often dosage reductions or treatment delays are required primarily due to hematologic toxicity. In the phase I study reported by Flaherty KT et al,[9] neutropenia was the dose-limiting toxicity and there was a relatively small incidence of grade 3 neutropenia (12%) and anemia (7%). Surprisingly in the single arm phase II study where palbociclib was also given as monotherapy, neutropenia was significantly higher and grade 3/4 neutropenia, anemia, and thrombocytopenia were reported in 51%, 5%, and 22% of patients, respectively. Of note, 24% of patients had treatment interruption and 51% had dose reductions, all due to cytopenias.[10]

In the PALOMA-1 study[11], the most common grade 3/4 toxicities were also hematologic. What seemed to be unexpected was the finding that although grade 3/4 neutropenia was reported in 54% of patients in the experimental arm, no cases of febrile neutropenia or neutropenia-related infections were seen. Among the nonhematologic all-grade AEs, the most common were fatigue (40%), nausea (25%), arthralgia (23%), and diarrhea (21%). Importantly, 43% of patients enrolled had received previous chemotherapy in the neoadjuvant or adjuvant setting.

In the PALOMA-3 study[13] the toxicity profile was not different and neutropenia was the most common adverse event occurring in 78.8% of patients receiving palbociclib-fulvestrant (any grade). Grade 3/4 neutropenia occurred in 62% of patients in the palbociclib arm compared with 0.6% in the placebo arm. In this study, low rates of neutropenia-related complications and

febrile neutropenia were also confirmed and were reported in 0.6% of patients in each arm.

Remarkably, 31.6% of patients required dosage reduction of palbociclib.

1.3. Minorities enrollment in clinical trials

The National Institute of Health (NIH) guidelines on the inclusion of women and minorities in clinical trials published in 1994 and updated in 2001 called for the initiation of programs and support for outreach efforts to recruit underrepresented groups into clinical trials.[14] Although these efforts have led to increased participation in some instances of previously excluded groups onto clinical trials, minority populations continue to be consistently underrepresented. In addition there is a lack of appreciation of genetic factors particular to Asian, African-American, Hispanic, and other ethnic communities.[15] This diversity gap can lead to sub-optimal development of new medicines, compromise the generalization of clinical trial results and further exacerbate minority health disparities.

The ability to trust and apply the results of a clinical trial, as well as transfer them into clinical practice, is related to the type and number of patients enrolled in that trial. If trials do not include minorities, then there is a question of whether or not the results of the studies are relevant to everyone across the board. According to a 2011 report from the conference "Dialogues on Diversifying Clinical Trials," sponsored by the FDA, African Americans represent 12% of the U.S. population but only 5% of clinical trial participants and Hispanics make up 16% of the population but only 1% of clinical trial participants.

1.4. Neutrophil count in African Americans

Benign ethnic neutropenia (BEN) is a condition used to describe individuals with neutrophil counts less than $1.5x10^9$cells/L in the absence of other causes.[16] It is common in people of African ancestry, including African Americans, and identifies a group (estimated in 50% of African Americans) with low absolute neutrophil count (ANC) but no increased risk of agranulocytosis or infection. Published evidence implicates a polymorphism (SNP rs2814778 at chromosome 1q23.2) in the Duffy Antigen Receptor Chemokine (DARC) gene in the pathophysiology of BEN.[17]

An ANC cutoff at $1.5x10^9$ cells/L for trial enrollment for African American patients when many have ethnic neutropenia may not be necessary.[18] Currently there are insufficient data to indicate that individuals with BEN would face a higher risk of febrile neutropenia greater than those without BEN. In a recent pilot study led by a group of investigators from the University of Maryland (not published yet), 12 African American patients with BEN and schizophrenia received clozapine (associated with neutropenia) safely and successfully continued despite low baseline ANC and outside current guidelines. In addition it has been reported that African American women with early breast cancer have lower white blood count (WBC) after chemotherapy and longer duration of treatment resulting in lower dose intensity of treatment which can contribute to observed racial differences in breast cancer survival. In this retrospective study there was no mention to an increased risk of febrile neutropenia in African American women compared to white.[19]

African American women have been underrepresented in clinical trials with palbociclib. This may be partially explained by rigid requirements for minimal WBC numbers (absolute neutrophil

count of 1500/mm^3 or higher). In the clinical trials where palbociclib was used for treatment of advanced breast cancer and have been published thus far, in PALOMA-1 there is no demographics available for the race/ethnicity of the participants, and in PALOMA-3 there is mention that 5.8% of patients enrolled in the experimental arm self-identified as black or other. Therefore conclusions regarding the rate of neutropenia and febrile neutropenia in African American patients treated with palbociclib cannot be safely extrapolated from the trials previously discussed.

1.5. Metabolite and exosomal signature of endocrine resistance

Metabolomics is a novel “omics” tool with promising clinical applications including breast cancer[20]. Onco-metabolites identified in blood, tissue or urine can be used as biomarkers of cancer[21,22]. While the metabolite signature of endocrine resistant breast cancer is not well understood, we have identified an increased dependence on glutamine metabolism in endocrine resistant breast cancer cell models[23]. Metabolic profile of serially collected blood samples have enabled detection of breast cancer relapse[24]. In this correlative study, untargeted metabolomics analysis of serum will allow identification of metabolite markers of endocrine resistance by comparing metabolite profile of responders to that of non-responders. Furthermore, clinical data such as diabetes, body mass index (BMI) or cardiovascular history will be helpful in stratifying our findings.

In breast cancer, exosomes (30-120 nm structures that are derived from cell membranes) have been suggested as a means of cell-to-cell communication that can be deregulated[25]. Exosomes are present in most human body fluids, including blood plasma/serum, saliva, breast milk, cerebrospinal fluid, urine and semen). These vesicles contain multiple proteins, DNA, mRNA, miRNA, long non-coding RNA, and even genetic materials of viruses or prions[26]. Characterization of exosomes can be useful as predictive biomarker signatures of drug resistance in the clinic[27,28]. Preliminary studies in our laboratory show distinct contents in exosomes derived from endocrine sensitive versus resistant cells.

1.6. Study Rationale

The proposal of this study is to evaluate the hematological safety of palbociclib in combination with letrozole or fulvestrant in African American women with hormone receptor positive HER2 negative advanced breast cancer. Currently there are insufficient data to describe the hematological safety for these individuals who have a high incidence of BEN.

We propose to lower the ANC cutoff for the enrollment of African American patients to 1000/mm^3 or higher. The standard lower limit of ANC of 1500/mm^3 for initiation of treatment in this population has been previously challenged by other authors.[18,29] We will follow the recommended guidelines for management of neutropenia and dose adjustments. In addition we will do correlative studies looking at metabolite biomarkers and exosomal signature of endocrine resistance.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

To evaluate the hematological safety of palbociclib with letrozole or fulvestrant in African American women with hormone receptor positive HER2 negative advanced breast cancer. Use of anastrozole or exemestane permitted in the event of letrozole intolerance.

Hematological safety is defined as a composite endpoint of episodes of febrile neutropenia and treatment discontinuation due to neutropenia according to current recommendations for management of neutropenia.

Secondary Objectives

1. To evaluate delays in palbociclib therapy attributed to neutropenia
2. To evaluate dose reductions in palbociclib therapy attributed to neutropenia
3. To evaluate grade 3/4 neutropenia
4. To evaluate the efficacy of palbociclib with letrozole or fulvestrant in African American women with HR positive HER2 negative advanced breast cancer with evaluable disease. Use of anastrozole or exemestane permitted in the event of letrozole intolerance.
5. To describe metabolite and exosomal signature and evaluate correlations with disease response
6. To describe baseline ANC prior to cancer diagnosis and the Duffy Null polymorphism (SNP rs2814778 at chromosome 1q23.2) and explore correlations with hematological safety

2.2. Endpoints

Primary Endpoint

Proportion of patients who complete planned oncologic therapy without the development of a hematological event defined as episodes of febrile neutropenia and treatment discontinuation due to neutropenia according to current recommendations for management of neutropenia.

If a patient comes off study prior to cycle 1 day 14, that patient will be replaced.

There are different definitions of febrile neutropenia but for study purpose this will be defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0: “ANC less than 1000/mm^3 with a single temperature of >38.3 degrees Celsius (101 degrees Fahrenheit) or a sustained temperature of 38 degrees Celsius (100.4 degrees Fahrenheit) for more than one hour.”

Planned oncology therapy is defined as completion of one year of therapy for advanced breast cancer in the absence of disease progression or cessation of study drug due to progressive disease or non-hematological toxicity.

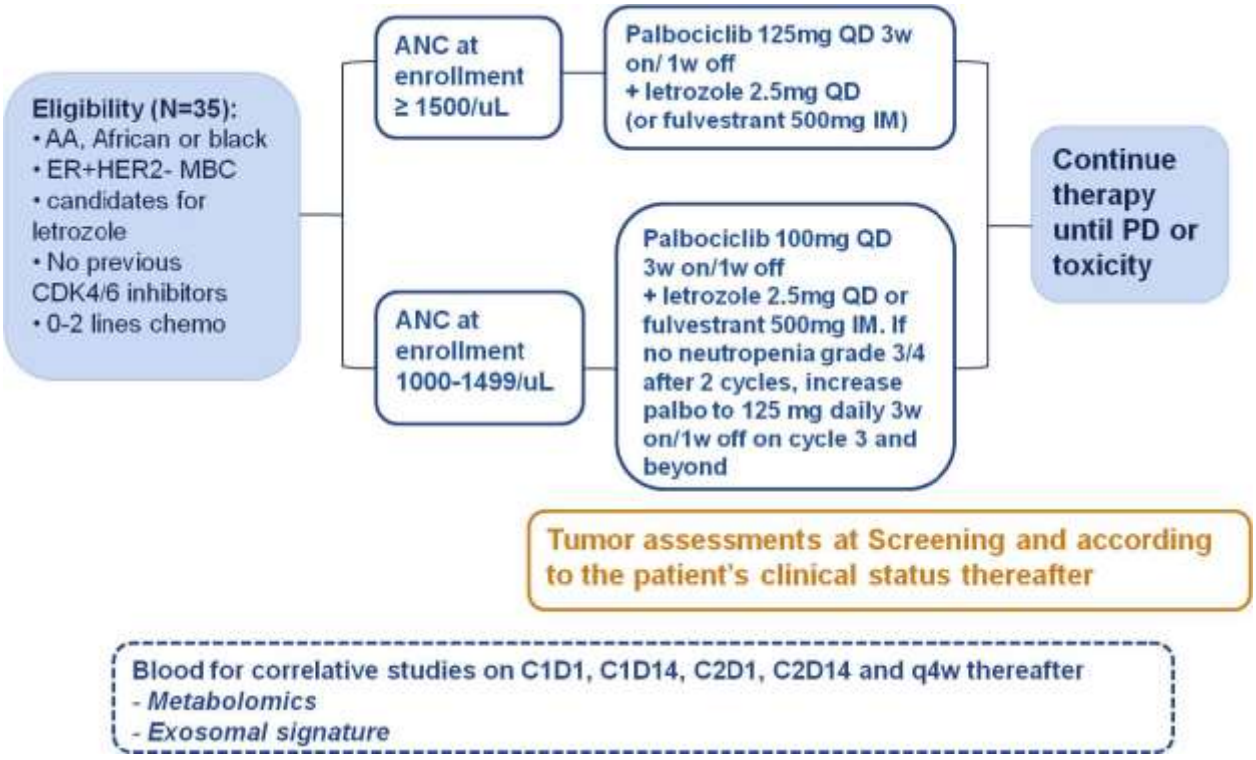
Secondary Endpoints

1. Number of patients who required dose delays in palbociclib attributed to neutropenia.
2. Number of patients who required dose reductions in palbociclib therapy attributed to neutropenia
3. Rate of grade 3/4 neutropenia

4. Clinical Benefit Rate (CBR), for those with evaluable disease, defined as the percentage of patients who achieved complete response, partial response and stable disease at 24 weeks
5. To evaluate correlations between metabolite and exosomal signature with disease response
6. To evaluate correlations between baseline ANC prior to cancer diagnosis and the Duffy Null polymorphism (SNP rs2814778 at chromosome 1q23.2) with hematological safety

3. STUDY DESIGN

Figure 1. Study design



This is a phase II, single arm, multicenter clinical trial.

Eligible patients will be self-identified Black, African or African American women with HR positive and HER2 negative advanced breast cancer. Patients will have histologically or cytologically proven diagnosis of adenocarcinoma of the breast (locoregionally recurrent or metastatic disease) and will be candidates to receive letrozole or fulvestrant for their advanced disease. Use of anastrozole or exemestane permitted in the event of letrozole intolerance.

Patients will be enrolled and will continue to receive treatment with palbociclib until disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, or completing 12 months on study, whichever occurs first. If a patient comes off study because she completed 12 months of palbociclib/letrozole or fulvestrant on study she can continue commercial drugs at the treating physician's discretion. Use of anastrozole or exemestane permitted in the event of letrozole intolerance.

Patients will undergo adverse events (AE) monitoring as per local practice. Adverse events will

be characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), and seriousness. All grades, all causality AEs and all serious adverse events (SAEs) will be recorded in the case report forms (CRF). All deaths occurring up to 28 days after palbociclib is discontinued will be recorded.

Hematology laboratory data will be recorded every 2 weeks for the first 2 cycles of therapy, then monthly at the start of each cycle thereafter. Recommendation for monitoring neutropenia available in the label and dose modification tables will be followed. Retreatment criteria are based on time to recovery of neutrophil count. The clinical actions taken as a result of Grade 3 neutropenia, including the use of G-CSF, if any, will be recorded.

Tumor response will be assessed as per local practice and only investigator tumor assessments will be collected for those who have evaluable disease. The date of tumor progression will be recorded.

3.1 Duration of therapy

Treatment will continue until participation and study therapy is no longer in the patient's best interest. Reasons for withdrawing a patient include, but are not limited to:
- Disease progression
- The occurrence of an adverse event or a concurrent illness. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.
- A patient's request to end participation
- A patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent.

Patients will be followed on study for a maximum of 12 months. If there are no reasons for withdrawing a patient at 12 months, patient can continue off study on the same therapy at the physician's discretion.

4. PATIENT SELECTION

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Self-identified Black, African or African American women of ≥ 18 years of age with proven diagnosis of advanced breast cancer (locoregionally recurrent or metastatic disease), either from the primary or a metastatic site.

2. Post-menopausal status defined by: a) age ≥60 years; b) age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or

physiological cause; c) documented bilateral oophorectomy; d) medically confirmed ovarian failure OR

   a. pre/peri-menopausal, ie, not meeting the criteria for being postmenopausal who are also receiving ongoing treatment with LHRH agonists (goserelin or leuprolide); the first injection should occur at least two weeks before study start.

3. ER-positive and/or PR-positive tumor (≥1% positive stained cells) based on local laboratory results

4. HER2-negative breast cancer based on local laboratory results (test to be used as per local practice). HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.

5. Patients must be appropriate candidates for letrozole therapy in any line of therapy or for fulvestrant for second line of therapy or beyond. Use of anastrozole or exemestane permitted in the event of letrozole intolerance.

6. Must have received no more than 2 lines of chemotherapy for the treatment of breast cancer, and one for the treatment of advanced breast cancer.

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 (Appendix 1)

8. Adequate bone marrow function:
   a. Absolute Neutrophil Count (ANC) ≥ 1,000/mm^3 (1.0 x 10^9 /L);
   b. Platelets ≥100,000/mm^3 (100 x 10^9 /L);
   c. Hemoglobin ≥9 g/dL (90 g/L).

9. Adequate liver function

   - AST and/or ALT ≤3 x ULN (≤5.0 x ULN if liver metastases present);
   - Alkaline phosphatase ≤2.5 x ULN (≤5.0 x ULN if bone or liver metastases present);
   - Total serum bilirubin ≤1.5 x ULN (≤3.0 x ULN if Gilbert's disease).

10. Adequate renal function
    - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 mL/min.

11. Resolution of all acute toxic effects of prior therapy, including radiotherapy to grade ≤1 (except toxicities not considered a safety risk for the patient) and recovery from surgical procedures.

12. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

13. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Current use of food or drugs known to be potent inhibitors or inducers of CYP3A4

2. Known hypersensitivity to letrozole, anastrozole, exemestane, or fulvestrant, or any of its excipients, or to any palbociclib excipients. If hypersensitivity to letrozole, anastrozole, exemestane, or fulvestrant, patients will be allowed to go on study as long as they don't have hypersensitivity to the endocrine therapy they will receive.

3. Active uncontrolled or symptomatic brain metastases. Previously treated and clinically stable, as per Investigator's judgment, brain metastases are permitted.

4. Previous CDK4/6 inhibitor

5. Other severe acute or chronic medical or psychiatric condition, including recent or active suicidal ideation or behavior, 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.

6. Pregnant or lactating patients. Patients of childbearing potential must agree to avoid pregnancy during study treatment and for at least two weeks after the last dose of the study drug.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Following full assessment and determination that the patient meets all eligibility criteria and has given informed consent for study participation, the investigator or designee will contact the study principal investigator (PI) or designee and request study enrollment. A patient identification number will be assigned, which must be used on all CRF pages and on all documentation and correspondence referencing that patient.

5.2. Compliance

Patients will be required to return all bottles of palbociclib at the beginning of each clinical visit for drug accountability.

Drug accountability will be performed at every clinical visit prior to dispensing drug supply for the next cycle(s). The number of remaining capsules will be documented and recorded to assess compliance.

5.3. Drug Supplies

The investigational drug used in the course of this trial is palbociclib (IBRANCE®).

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. Palbociclib

Palbociclib will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. The oral drug formulation will be supplied in High Density Polyethylene (HDPE) bottles containing 75 mg, 100 mg, or 125 mg capsules.

5.3.1.2. Letrozole

Commercially available letrozole will be used. Locally obtained commercial supplies of letrozole will be used in accordance with local regulations.

5.3.1.3. Fulvestrant

Commercially available fulvestrant will be used. Locally obtained commercial supplies of fulvestrant will be used in accordance with local regulations.

5.3.1.4 Anastrozole

Commerically available anastrozole will be used. Locally obtained commercial supplies of anastrozole will be used in accordance with local regulations.

5.3.1.5 Exemestane

Commercially available exemestane will be used. Locally obtained commercial supplies of exemestane will be used in accordance with local regulations.

5.3.2. Preparation and Dispensing - Palbociclib

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 clinical visit. Bottles contain 21 capsules.

Unused drug and/or empty bottles should be returned to the site at the next clinical visit. Unused returned medication MUST NOT be re-dispensed to patients.

Palbociclib 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 a single 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.

5.3.3. Administration

5.3.3.1. Palbociclib

Palbociclib will be administered orally once a day at 125 mg/day for 21 days followed by 7 days off treatment for each 28-day cycle (Schedule 3/1). For patients enrolled with baseline ANC between 1000 and 1499/uL, initial dose of palbociclib will be 100mg once daily for 21days followed by 7 days off treatment. If no grade 3 or 4 neutropenia is observed in the two first cycles, dose will be increased to 125 mg/day on the third cycle and then follow general dose modifications.

General rules for palbociclib administration:
- Palbociclib should be taken with food.
- Palbociclib capsules should be swallowed whole (do NOT chew, crush or open 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 who miss a day's dose entirely 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 the Medication Errors (Section 8.3.1) for further details on medication errors and overdose.

5.3.3.2. Letrozole

Letrozole will be administered orally at 2.5 mg once daily as continuous daily dosing schedule according to product labeling and in compliance with its local prescribing information.

5.3.3.3. Fulvestrant

Fulvestrant will be administered as intramuscular injections at the initial dose of 500 mg on days 1, 15, and 29, and as maintenance dose of 500 mg once every 28 days, according to product labeling and in compliance with its local prescribing information.

5.3.3.4. Anastrozole

Anastrozole will be administered orally at 1mg once daily as continuous daily dosing schedule according to product labeling and in compliance with its local prescribing information.

5.3.3.5. Exemestane

Exemestance will be administered orally at 25mg once daily as continuous daily dosing schedule according to product labeling and in compliance with its local prescribing information.

5.3.4. Recommended Dose Modification

In the event of significant treatment-related toxicity, administration of palbociclib may need to be adjusted as described in the following sections. As letrozole, anastrozole, exemestane, and fulvestrant doses cannot be reduced, letrozole, anastrozole, exemestane, or fulvestrant treatment may be interrupted in the case of toxicity as described below.

Depending on the nature of the toxicity observed, treatment interruption may be required for one or both study drugs in the combination. In the event treatment interruption is deemed necessary for just one of the study drugs in the combination, treatment with the other drug may continue as planned if deemed clinically appropriate.

In case of palbociclib dose delays, administration of letrozole, anastrozole, exemestane, or fulvestrant may continue according to the pre-planned schedule.

In case of palbociclib permanent discontinuation, the patient will undergo End of Study visits as described in Schedule of Activities (Table 5). Continuation of letrozole, anastrozole, exemestane, or fulvestrant would be off study per treating physician discretion.

5.3.4.1. Dosing Interruptions/Delays – Recommendations for Palbociclib

Patients experiencing the following adverse events may have their treatment with palbociclib interrupted/delayed until criteria for retreatment are met (Section 5.3.4.2).

Patients should not hold or discontinue palbociclib for non-hematological side effects potentially or likely related to concomitant letrozole, anastrozole, exemestane, or fulvestrant therapy (eg, Grade 3 or long lasting Grade 2 joint pain) as per the investigator's judgment.

Depending on when the AE resolves, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay in the initiation of the subsequent cycle.

Doses omitted for toxicity are not replaced within the same cycle.

Doses should be held until toxicity resolution as per Retreatment Criteria (Section 5.3.4.2).

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions (Section 5.3.4.3).

In the case of Grade 3 neutropenia, consider repeating complete blood count (CBC) monitoring within one week in accordance with best local practice and report in the CRF in order to

document the level of neutropenia and the time to recovery of neutrophils to ≥1,000 cells/mm^3. Retreatment criteria are based on time to recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modification tables. The clinical actions taken as a result of Grade 3 neutropenia, including the use of G-CSF, if any, will be recorded.

If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

5.3.4.2. Retreatment Criteria - Palbociclib

Retreatment with palbociclib following treatment interruption for treatment related toxicity 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
- Grade ≥3 non-hematologic AEs (including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical management) have recovered to grade≤1 or baseline or, at the investigator discretion, grade≤2 if not considered a safety risk for the patient

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be increased as per best clinical practice.

If the retreatment parameters are met within 3 weeks of dose interruption, palbociclib may be resumed at the same dose.

If the retreatment parameters have not been met after > 3 weeks of dose interruption, the patient should permanently discontinue palbociclib treatment. However, if a patient is deemed to be suitable for a lower dose of palbociclib, treatment may be resumed at a lower dose at the investigator's discretion (see below for suggested dose adjustments).

5.3.4.3. Dose Reductions - Palbociclib

Following dose interruption or cycle delay the palbociclib, dose may need to be reduced when treatment is resumed. Available dose levels in case of palbociclib dose reduction are reported in Table 2.

Table 2. Available dose levels

Recommended Dose Modification for Adverse Reactions Dose Level	Dose
Recommended starting dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*

*If further dose reduction below 75 mg/day is required, discontinue the treatment.

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

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

All dose modifications/adjustments must be clearly documented in the CRF along with reasons for dose modification/adjustment.
Palbociclib recommended dose modifications for treatment related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 3 and 4.

Table 3. Dose modification and management for hematologic toxicities

CTCAE grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3 neutropenia (ANC<1000/mm^3), thrombocytopenia (PLC < 50,000/mm^3) or anemia (Hgb < 8g/dL)	No dose adjustment is required. Consider repeating CBC monitoring one week later. Withhold initiation of next cycle until recovery to Grade ≤2.
Grade 3 neutropenia (<1000 to 500/mm^3) + fever ≥38.5ºC and/or infection	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤2 (≥1000/mm^3). Resume at next lower dose.
Grade 4 neutropenia (ANC<500/mm^3), thrombocytopenia (PLC < 25,000/mm^3) or anemia (life threatening consequences)	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤2. Resume at next lower dose.

Table 4. Dose Modification and Management – Non-Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-hematologic toxicity (if persisting despite medical treatment)	Withhold until symptoms resolve to: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the next lower dose.

5.4. Drug Storage

Palbociclib, letrozole, anastrozole, exemestane, and fulvestrant should be stored in original containers and in accordance with the FDA approved drug label.

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under recommended storage

conditions and in accordance with applicable regulatory requirements.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the storage requirements for take home medications including how to report temperature excursions.

5.5. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of palbociclib drug supply. Patients will be required to return all bottles of palbociclib at the beginning of each clinical visit for drug accountability (see also Section 5.2 Compliance).

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site).

The site will be responsible for drug destruction. The investigators must ensure that the drug is destroyed in compliance with applicable environmental regulations, and according to their approved institutional practices. All destruction must be adequately documented.

5.6. Concomitant Medication(s)

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator.

All concomitant medications required to clinically manage patients while they are receiving palbociclib therapy are permitted unless specified below in Sections 5.6.1 and 5.6.2. Documentation of these medications will not be collected on the CRF but will need to be available from the patient's medical record upon request by the Sponsor.

An exception will be the use of growth factors including granulocyte colony stimulating factor (GCSF). Growth factors should not be used for upfront prophylaxis, but may be used to treat neutropenia associated with clinically significant complications, and should follow established ASCO guidelines. Use outside this indication should be discussed

with the study PI. Dose reduction is the preferred initial method to address neutropenia rather than GCSF. GCSF use will be documented in the CRF as well as other agents used to treat/manage AEs while on therapy.

Immunizations (inactivated vaccines, including inactivated influenza vaccine) prior to initiation of therapy will be administered as clinically indicated and documented in CRF.

Proton pump inhibitors (PPI): In a drug interaction trial in healthy subjects, coadministration of a single 125 mg dose of palbociclib with multiple doses of the PPI rabeprazole under fed conditions decreased palbociclib Cmax by 41%, but had limited impact on AUC inferior (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. In another healthy subject study, coadministration of a single dose of palbociclib with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUC inf and Cmax by 62% and 80%, respectively, when compared to a single dose of palbociclib administered alone.

Surgery is allowed during protocol therapy, however it is suggested to avoid nadir of counts at time of surgery. Patients pursuing surgery must hold palbociclib therapy 7 days before the surgery and up to 3 weeks after surgery. Patients may resume palbociclib therapy once satisfactory wound healing and recovery have occurred. Patients should continue endocrine therapy if palbociclib is held for surgery.

5.6.1. Prohibited Medications

Anticancer agents: No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than letrozole, anastrozole, exemestane, or fulvestrant will be permitted during the 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 strong CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans.

The concurrent use of ***strong 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 ***strong CYP3A inducers***, including carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort, are not allowed in the study.

5.6.2. Medications Not Recommended

Alternative therapies should be considered whenever possible for the following treatments:

CYP3A Substrates: caution must be exercised in patients receiving palbociclib in combination with drugs that are predominantly metabolized by CYP3A. In particular, co-administration of

palbociclib with CYP3A4 substrates with narrow therapeutic index including, but not limited to alfentanil, aripiprazole, cyclosporine, ergotamine, fentanyl, halofantrine, pimozide, quinidine, sirolimus, tacrolimus, triazolam are not recommended during the treatment with palbociclib.

The use of herbal medicines is not recommended.

6. STUDY PROCEDURES

6.1. Schedule of events

Study procedure/ assessment	Screening	Treatment: one cycle =28 days			End of Treatment[c]	End of Study[c]
		Cycles 1 and 2		Cycles ≥ 3		
Study day	Within 28 days prior to study entry	Day 1	Day 14			
Time Window		+/- 2 days	+/- 2 days	+/- 2 days	+/- 7 days	+/- 7 days
Procedures at screening[a]						
Informed Consent[d]	X					
Eligibility criteria checklist[e]	X					
Registration[f]	X					
Medical History[g]	X					
CBC with diff prior to cancer diagnosis (if available)[s]	X					
Procedures at screening and on study						
Physical examination/ Clinical Visits[b]	X	Per routine clinical practice				
Comorbidities (including DM and CVD)[h]	X	Per routine clinical practice				
ECOG PS[i]	X	Per routine clinical practice			X	
BMI	X	Per routine clinical practice			X	
Concomitant Meds Review	X	X		X	X	
Adverse Events[j]	X	X	X	X	X	X
Medication Diary[k]		X		X	X	
Treatments						
Palbociclib[l]		Orally once daily from D1 to D21 of each cycle (schedule 3/1)				
Letrozole[m] or		Orally once daily (schedule continuous dosing) Or				

Fulvestrant[t]		500mg intramuscular injection on days 1, 15, and 29, and 500mg once every 28 days thereafterc				
Laboratory tests/ Imaging/ Correlative Blood Studies						
Tumor assessment[n]	X	Per routine clinical practice				
Hematology (CBC with diff)[o]	X	X	X	X	X	X
Chemistry[p]	X	Per routine clinical practice				
Pregnancy test[q]	X					
Research labs[r]		X	X	X	X	X

Footnotes to the schedule of activities:

[a]**Screening:** All assessments should be performed within 28 days prior to study entry.

[b]**Clinical Visits:** clinical visits will be conducted as per local practice and as clinically indicated. Physical Examination includes general clinical examination of major body systems.

[c]**End of Study:** The End of Treatment visit will be conducted when palbociclib is permanently discontinued for any reason. The indicated assessments are to be obtained if not completed in the last week of therapy. The End of Study visit will occur 28 days after last dose of palbociclib or after patient comes off study, whichever comes last. End of Study visit will be completed also in case a patient will continue on commercial palbociclib. Adverse events should be followed up until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable”.

[d]**Informed Consent**: Must be obtained prior to undergoing any study specific procedures.

[e]**Eligibility Criteria Evaluation:** Patients must meet all of the eligibility criteria reported in the protocol and checklist must be filled.

[f]**Registration:** Patient identification number will be attributed to each patient.

[g]**Medical History:** Medical history includes history of disease process other than oncology (active or resolved). It should also include Oncological history with date of primary diagnosis, information on prior anti-tumor treatments and radiotherapy, and oncologic surgeries.

[h]**Comorbidities** including diabetes mellitus (DM) and cardiovascular disease (CVD) should be documented as screening and as clinically indicated. This should be part of the clinical visits.

[i]**ECOG Performance Status**: To be performed at Screening, as per routine clinical practice during the treatment, and at the end of treatment. ECOG performance scale is available in Protocol Appendix 1.

[j]**Adverse Events**: Patients must be followed for Adverse Events (AEs) from the time they signed the informed consent until 28 days after the last treatment administration or until all palbociclib-related toxicities have resolved, whichever is later. 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. AEs should be documented and recorded at each clinical visit using NCI CTC-AE version 4.03 from the time the patient has taken at least one dose of study treatment through last patient visit. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of the investigational product. SAEs experienced by a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

[k]**Patient Medication Diary:** patient will receive a new medication diary on day 1 of each cycle of and will return it filled and signed at the end of each cycle

[l]**Palbociclib Administration:** Palbociclib will be administered orally once daily at the starting dose of 125 mg, on Day 1 to Day 21 followed by 7 days off treatment (Schedule 3/1). The patient will receive drug supply at the clinical site that will be sufficient for 1-3 months of treatment depending on the decision of the treating physician.

[m]**Letrozole, Anastrozole, and Exemestane Administration:** Letrozole will be administered orally once

daily at the dose of 2.5 mg (continuous daily dosing schedule). Anastrozole will be administered orally once daily at the dose of 1mg (continuous daily dosing schedule). Exemestane will be administered orally once daily at the dose of 25mg. Locally obtained supplies of letrozole, anastrozole, and exemestane will be used.

[n]**Tumor Assessments:** Tumor assessments are to be performed at Screening and as per local practice and according to the patient's clinical status thereafter. Tumor assessment evaluation will be conducted as per local guidelines. Only investigators' assessments will be recorded in the CRF.

[o]**Hematology:** To include complete blood count (CBC) with differential. To be performed to check patient's eligibility at Screening, every 2 weeks (Days 1 and 14) of the first 2 cycles, then monthly on Day 1 of each subsequent cycle of treatment with palbociclib and at the end of treatment. In the case of Grade 3 neutropenia consider repeating complete blood count monitoring one week later in accordance with best local practice and report in the CRF in order to document the ANC value at the time of severe neutropenia as well as the time to recovery of neutrophils to ≥1,000 cells/mm^3. Retreatment criteria are based on time to recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modification tables. If granulocyte-colony stimulating factors (G-CSF) and/or antibiotics are administered, their use will be documented on the CRF. For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, complete blood counts for subsequent cycles may be performed every 3 months only, prior to the beginning of a cycle and as clinically indicated.

[p]**Blood Chemistry:** To be performed to check patient's eligibility at Screening, and as per routine clinical practice thereafter. Only laboratory data at Screening will be recorded on the CRF.

[q]**Pregnancy Test (serum or urine):** Required for women of childbearing potential

[r]**Research labs:** refer to Study Procedures Manual for collection, labeling, processing and shipping instructions.

[s]**CBC with diff prior to cancer diagnosis:** this information will be collected if available

[t]**Fulvestrant administration:** will be administered as intramuscular injections at the initial dose of 500 mg on days 1, 15, and 29, and as maintenance dose of 500 mg once every 28 days. Locally obtained commercial supplies of fulvestrant will be used.

6.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons why patients may discontinue or be withdrawn from the protocol may be due to the following:

- Adverse events
- Intercurrent illness
- Disease progression
- Patient is non-compliant
- Patient is lost to follow-up
- Withdrawal of consent

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product, request the patient to return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

7. ASSESSMENTS

7.1. Safety Assessments

Safety assessment will consist of monitoring of all adverse events (AEs), including serious adverse events (SAEs) at every clinical visit and monitoring of hematology to be performed to check patient's eligibility at Screening, every 2 weeks (Days 1 and 14) of the first 2 cycles, then monthly on Day 1 of each subsequent cycle of treatment with palbociclib and at the end of treatment. In the case of Grade 3 neutropenia consider repeating complete blood count monitoring within one week in accordance with best local practice and report in the CRF in order to document the ANC value at the time of severe neutropenia as well as the time to recovery of neutrophils to ≥1,000 cells/mm^3. Retreatment criteria are based on time to recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modification tables.

Other procedures as necessary according to standard of care and in accordance with each site's institutional guidelines will be assessed to monitor for adverse events related to the underlying disease, treatment with palbociclib or treatment with letrozole, anastrozole, exemestane, or fulvestrant or supportive therapies (see Section 8 for Adverse Event Reporting).

Information generated from these assessments may also be used to determine if an adverse event occurred as defined in Section 8.

7.1.1. Physical Examination

A full physical examination of all major body systems will be required at Screening. Symptom directed physical examinations will be performed as per routine clinical practice during the study. Only physical examination at Screening will be recorded on the CRF. Physical examinations performed during treatment will need to be available from the patient's medical record upon request by the Sponsor.

The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scale will be required at Screening, as per routine clinical practice during the study, and at the end of treatment. Data collected at Screening and at the end of treatment will be recorded on the CRF. Other ECOG PS assessments during study will need to be available from the patient's medical record upon request by the Sponsor. ECOG PS scale is available in Protocol Appendix 1.

7.1.2. Laboratory Safety Assessments

Blood tests will include the following:

1. Hematology panel: complete blood count with differential
2. Blood chemistry panel: ALT, ASL, alkaline phosphatase, total bilirubin, serum creatinine

Blood tests will be drawn at the time points described in Table 5 (Schedule of Activities) and analyzed at local laboratories.

Hematology panel (includes complete blood count with differential) will be performed to verify patient's eligibility at Screening, every 2 weeks (Days 1 and 14) of the first 2 cycles of therapy, then monthly on Day 1 of each subsequent cycle of treatment with palbociclib and at the end of treatment. Laboratory data will be recorded on the CRF.

In the case of Grade 3 neutropenia, consider repeating complete blood count monitoring within one week in accordance with best local practice and report in the CRF in order to document the level of neutropenia and the time to recovery of neutrophils to ≥1,000 cells/mm^3. Retreatment criteria are based on time to recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modification tables. The clinical actions taken as a result of Grade 3 neutropenia, including the use of G-CSF, if any, should be recorded.

Blood Chemistry will be performed to verify patient's eligibility at Screening, and as per routine clinical practice thereafter. Only laboratory data at Screening will be recorded on the CRF. During the study blood chemistry data will not be collected on the CRF but will need to be available from the patient's medical record upon request by the Sponsor. In the case a laboratory abnormality meets the definition of AE, as determined by the investigator and according to Adverse Event Reporting Section 8, this must be captured on an AE CRF page.

7.2. Tumor Assessments

Tumor assessments are to be performed at Screening and as per routine clinical practice and according to the patient's clinical status thereafter (see also Schedule of Activities, Table 5). Tumor assessment evaluation will be conducted as per local practice at each institution.

Only investigators' assessments will be recorded in the CRF.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be

required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should 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 palbociclib through last patient visit.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:
- Abnormal test findings (see section 8.4)
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Drug abuse
- Drug dependency

Additionally, they may include the signs and symptoms resulting from:
- Drug overdose
- Drug withdrawal
- Drug misuse

- Drug interactions
- Extravasation
- Exposure during pregnancy
- Exposure via breast feeding
- Medication error
- Occupation exposure
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section in the CRF

Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.3.1. Medication Errors

Medication errors may result from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength.

Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the Sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:
- Medication errors involving patient exposure to the investigational product
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error should be captured on the medication error version of the adverse event (AE) page and, if applicable, any associated adverse event(s) are captured on an adverse event (AE) CRF page.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:
- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or Sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.5. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:
- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTC Grade 5 (see Section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section on SAE Reporting Requirements).

8.6. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:
- Rehabilitation facilities
- Hospice facilities
- Respite care (eg caregiver relif)
- Skilled nursing facilities
- Nursing homes
- Same day surgeries

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:
- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.7. Severity Assessment

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC), (Version 4.03 Publish Date: June 14, 2010).
Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.
In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.9. Withdrawal Due to Adverse Events (See Also Section on Patient Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.
When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.10. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the patient. In addition, each study patient will be questioned about AEs.

8.11. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.11.1 Serious Adverse Event Reporting Requirements

Reporting of Serious Adverse Events: Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), Principal Investigator will report to Pfizer by facsimile any Serious Adverse Event ("SAE," as defined below) for which reporting is required under this provision (as described below). Such SAEs are to be reported for (1) Study subjects who are assigned or, in the case of a blinded Study, possibly assigned to receive the Pfizer Product or (2) individuals otherwise exposed to the Pfizer Product as described below. Principal Investigator should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available.

Reporting Forms. Principal Investigator will report SAEs using one of the following forms: (1) a reporting form approved by the local regulatory authority, (2) a CIOMS form, (3) a Pfizer-provided *Investigator-Initiated Research Serious Adverse Event Form*, or (4) any other form prospectively approved by Pfizer. The *Reportable Event Fax Cover Sheet* provided by Pfizer must also be included with each SAE submitted.

a. SAE Definition. An SAE is any adverse event, without regard to causality, that is life-threatening (i.e., causes an immediate risk of death) or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity (i.e., substantial disruption of the ability to conduct normal life functions); or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

b. Exposure during Pregnancy, Exposure during Lactation, Occupational Exposure, and Lack Of Effect. Even though there may not be an associated SAE, exposure to the Pfizer Product during pregnancy, exposure to the Pfizer Product during lactation, and occupational exposure to the Pfizer Product are reportable, and lack of effect of the Pfizer Product may also be reportable. These requirements are further explained in the training material provided by Pfizer (see Pfizer-Provided Training, below). As used in this Agreement, the term SAE will be understood to include exposure during pregnancy, exposure during lactation, occupational exposure, and reportable instances of lack of effect.

c. Hy's Law Cases. Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable to Pfizer. If a Study subject develops abnormal values in aspartate transaminase (AST) or alanine transaminase or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case. As used in this Agreement, the term SAE will be understood to also include Hy's Law Cases.

d. Exclusions from SAE Reporting Requirements. Specifically excluded from the reporting

requirements for SAEs under this provision is any SAE identified in the Protocol as anticipated to occur in the Study population at some frequency independent of drug exposure, unless the Principal Investigator assesses such an event as related to the Pfizer Product.

e. SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Pfizer Product through 28 calendar days after the last administration of the Pfizer Product, or longer if so specified in the Protocol. In addition, if Principal Investigator becomes aware of an SAE occurring any time after the administration of the last dose of the Pfizer Product, Principal Investigator should report that SAE to Pfizer if the Principal Investigator suspects a causal relationship between the Pfizer Product and the SAE.

f. Follow-Up Information. Principal Investigator will assist Pfizer in investigating any SAE and will provide any follow-up information reasonably requested by Pfizer.

g. Regulatory Reporting. Reporting an SAE to Pfizer does not relieve Principal Investigator of responsibility for reporting it to appropriate regulatory authorities, if such reporting is required.

h. Pfizer-Provided Training. Pfizer will make available training material that provides information about the SAE reporting requirements for IIR studies. Principal Investigator will review this material and share it with any Study staff engaged in the reporting of SAEs.

8.11.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.11.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. CORRELATIVE STUDIES

[redacted]

[redacted]

[redacted]

The Duffy Null polymorphism (SNP rs2814778 at chromosome 1q23.2) is known to protect against *Plasmodium vivax* malaria and has been recently confirmed to be predictive of WBC and neutrophil count in African Americans.[17] Genotyping of the rs2814778 polymorphism will be done using targeted sequencing for those patients who have consented for it.

10. DATA ANALYSIS/STATISTICAL METHODS

10.1. Two stage design, Sample Size, Accrual and Study duration

The study is designed to assess the rate of completion of planned oncology therapy in the absence of a hematological event defined as episodes of febrile neutropenia and/or treatment discontinuation due to neutropenia. Planned oncology therapy is defined as completion of one year of therapy for advanced breast cancer in the absence of disease progression or cessation of study drug due to progressive disease or non-neutropenia toxicity.

There is no data about the current proportion of African American patients who meet the composite primary endpoint. In the phase II PALOMA-1 study 13% of patients discontinued drug due to adverse events.[11] Although it is not described what specific adverse event caused the treatment discontinuation, we can expect that a significant number of cases was caused by neutropenia as the majority of patients (54%) experienced grade 3 or 4 neutropenia. It is reported also that there were no cases of febrile neutropenia. It is mentioned in the product labeling that febrile neutropenia events have been reported in the IBRANCE® clinical program, but the rate of events is not reported. Therefore we estimate that if 80% or more of patients will be able to receive palbociclib for advanced breast cancer without developing febrile neutropenia or discontinuing drug due to neutropenia it will be clinically meaningful. Therefore we defined a completion rate if 80% as considered of clinical relevance, where as a completion rate of 60% is considered non clinically meaningful.

Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true

completion rate is 60% will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are 8 or fewer complete the therapy in the absence of a hematological event (defined as episodes of febrile neutropenia and/or treatment discontinuation due to neutropenia) in these 13 patients, the study will be stopped. Otherwise, 22 additional patients will be accrued for a total of 35. The null hypothesis will be rejected if 26 or more patients complete the therapy in the absence of a hematological event in 35 patients.

This design yields a type I error rate of 0.05 and power of 80% when the true completion rate is 80%. The intention-to-treat (ITT) population of this trial will be composed of patients who are actually enrolled and received at least one dose of palbociclib since they are on study.

We anticipate accruing 35 patients over 12 months across the 3 sites. Historically the three sites have experience in accruing African American patients into clinical trials. All patients will be followed for a maximum of 12 months. Study duration will have a maximum of 24 months.

10.2. Statistical Analysis Plan

The two-stage analysis will follow the design described in 10.1. An exact confidence interval of the completion rate based on binomial calculation will be obtained. We estimate there will be no more than 10% episodes of febrile neutropenia.

The outliers and data errors will be checked. Descriptive statistics will be used to characterize the demographic profile of the subjects. Frequency and percentages will be used to summarize categorical variables. Mean (SD) or median (interquartile range) based on the normalization of the data will be used to summarize continuous variables.

The incidence of hematological events during study treatment will be calculated, as well as the number of patients who required dose delays in palbociclib attributed to neutropenia, the number of patients who required dose reductions in palbociclib therapy attributed to neutropenia, the rate of grade 3/4 neutropenia.

For statistical purposes and for evaluation of the primary endpoint, patients who discontinue treatment for progressive disease, non-hematologic toxicity or other reasons (that do not include febrile neutropenia or other hematological toxicities) will be considered as having completed planned oncologic therapy."

Study drug administration will be described in terms of total and median number of weeks administered, doses, and reasons for deviation from planned therapy.

An exploratory subgroup analysis will be performed to see if the primary outcome differs between the patients with baseline ANC equal or higher than 1500/uL and the patients with baseline ANC between 1000 and 1499/uL. A second exploratory subgroup analysis will be performed for those patients who have available ANC before cancer diagnosis: baseline ANC prior to cancer diagnosis (equal or higher than 1500/uL versus below 1500/uL) will be correlated with primary outcome.

For those with evaluable disease, clinical benefit rate at 24 weeks will be calculated. CBR is

defined as the percentage of patients who achieved complete response, partial response and stable disease at 24 weeks.

We will calculate the mean (SD) of specific metabolites at each time point and graphically assess these measures over time with clinical response and hematological toxicity. The mean change in these variables from baseline to each follow-up point will be calculated. Generalized linear model will be utilized for the correlative analysis of clinical response and hematologic events.

10.3. Safety stopping rules

Early stopping rules will be incorporated for safety based on febrile neutropenia. If the rate of febrile neutropenia is 10% or higher in this population then this would be considered a regimen with intermediate risk for febrile neutropenia (10-20%) and consideration of prophylactic myeloid growth factors along with additional clinical trials should be given.

If 3 patients experience symptoms of febrile neutropenia related to the treatment, then the trial will be terminated. We will accept a rate of less than 10% for events of febrile neutropenia. With 35 patients enrolled, if 3 febrile neutropenia events are observed, the exact binomial 90% CI would be (2.38% to 20.69%). The probability of observing 3 or more febrile neutropenia events, for a range of true underlying rates, is summarized in Table 5, indicating for example, that if the true rate is as high as 10% then the study has a 0.69 probability of observing three or more febrile neutropenia events when 35 patients are treated, and if as high as 15% there is a 0.91 probability of having observed three or more.

If the rate of febrile neutropenia events is higher than 10%, the likelihood of detecting it is high.

Table 6. Probability of observing at least three febrile neutropenia, for a range of true underlying event rates, with n=35 patients.

				True probability of febrile neutropenia			
	0.03	0.04	0.05	0.06	0.07	0.1	0.15
Probability	0.09	0.16	0.25	0.35	0.45	0.69	0.91

10.4. Safety Analysis

Safety data will be summarized for all patients who received at least one dose of study medication.

10.5. Data Safety Monitoring Committee

As this study is an investigator initiated study utilizing FDA approved agents it is considered a moderate risk study which requires real-time monitoring by the PI and study team and semiannual reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at weekly disease group meetings and on monthly network disease group teleconferences. The investigators shall meet regularly to review toxicities and follow up on results of patients enrolled on the study.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 6 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB. E-mail notification from the PI will be sent to the DSMC Chair any time there is a major event or issue with the trial affecting patient safety or conduct of the trial. The DSMC Chair has the discretion to have the study reviewed by the DSMC sooner more frequently than every 6 months based on information received.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. In addition, all SAEs will be submitted to the DSMC at time of submission to IRB and/or Sponsor. Based on SAEs, the IRB retains the authority to close the study to further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC, then the Lombardi Cancer Center Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the Lombardi Cancer Center ADCR will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision.

11. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure

that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the IRB, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

12. DATA HANDLING AND RECORD KEEPING

12.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to an electronic data record. A CRF is required and should be completed for each included patient. The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. Blood chemistry laboratory data during the treatment period, ECGs, and concomitant medications will not be collected on the CRF; however, Pfizer retains the right to view source documents if needed (see Section 10 above). The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.
In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

12.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed

informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

13. ETHICS

13.1. Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB. All correspondence with the IRB/EC should be retained in the Investigator File. Copies of IRB approvals should be forwarded to Pfizer.
The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB and Pfizer in writing immediately after the implementation.

13.2. Ethical Conduct of the Study

This protocol will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).
In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.
When study data is compiled for transfer to Pfizer and other authorized parties, patient names, addresses and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients.

The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws. The informed consent/assent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent document(s) used during the informed consent process must be reviewed by the Sponsor, approved by the IRB before use, and available for inspection.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited she cannot reasonably be consulted, as permitted by the IRB and consistent with local regulatory and legal requirements, then the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide her own consent, the source documents must record why the patient did not provide consent (eg, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study- specific activity is performed, unless a waiver of informed consent has been granted by an IRB. The investigator will retain the original of each patient's signed consent/assent document

13.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

a. Emergency Modifications: Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

b. Single Patient/Subject Exceptions: Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator and the IRB.

c. Other Protocol Deviations/Violations: All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB.

According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:
• Is generally noted or recognized after it occurs
• Has no substantive effect on the risks to research participants
• Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
• Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:
• Has harmed or increased the risk of harm to one or more research participants.
• Has damaged the scientific integrity of the data collected for the study.
• Results from willful or knowing misconduct on the part of the investigator(s).
• Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

a. Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Minor deviations should be summarized and reported to the IRB at the time of continuing review. Major deviations should be summarized and reported to the Regulatory Affairs Coordinator who will submit to the IRB as soon as possible, but not more than 10 calendar days after acquiring information reasonably suggesting that a reportable (major) deviation has occurred.

b. Protocol Violations: Violations should be reported by study personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

13.5. Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

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LIST OF APPENDICES

Appendix 1. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

Appendix 2. List of abbreviations

AE	Adverse events
ANC	Absolute neutrophil count
BEN	Benign Ethnic Neutropenia
CBC	Complete blood count
CBR	Clinical benefit rate
CDK	Cyclin dependent kinase
CRF	Case Report Form
CVD	Cardiovascular disease
DLT	Dose-limiting toxicities
DM	Diabetes Mellitus
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen Receptor
FDA	Food and Drug Administration
HER2	Human epidermal growth factor receptor 2
HR	Hormone Receptor
HR	Hazard ratio
IRB	Institutional Board Review
NCI	National Cancer Institute
NIH	National Institute of Health
ORR	Overall response rate
PFS	Progression Free Survival
PI	Principal Investigator
PR	Progesterone Receptor
PR	Partial Response
PS	Performance status
Rb	Retinoblastoma
RP2D	Recommended phase 2 dose
SAE	Serious Adverse Event
SD	Stable Disease
SNP	Single Nucleotide Polymorphisms
TTF	Time to treatment failure
TTP	Time to treatment progression
WBC	White blood count

PATIENT MEDICATION DIARY *(Palbociclib + Letrozole, Anastrozole, or Exemestane)*
Study: Phase II Safety Study of Palbociclib with Letrozole or Fulvestrant in African American Women with Hormone Receptor Positive HER2 Negative Advanced Breast Cancer

Subject #: _____ Site: _____
Cycle #:_____ Current dose of palbociclib: _____mg

*Take one Palbociclib capsule with food on Days 1-21. Take one Letrozole, Anastrozole, or Exemestane tablet on Days 1-28. If you miss a day's dose entirely, you should **NOT** make it up the next day. If you inadvertently take 1 extra dose during a day, you should **NOT** take the next day's dose. Unused drug and/or empty bottles should be **RETURNED** to the site at the next study visit. Please record your diary daily. Always bring your completed patient diary to the clinic at **EACH** study visit.*

	Date taken (mm/dd/yyy)	**Palbociclib**	☐ Letrozole ☐ Anastrozole ☐ Exemestane	**Comments** *(Please use this section to write down explanation for any missed doses)*
Day 1	/ /	☐	☐	
Day 2	/ /	☐	☐	
Day 3	/ /	☐	☐	
Day 4	/ /	☐	☐	
Day 5	/ /	☐	☐	
Day 6	/ /	☐	☐	
Day 7	/ /	☐	☐	
Day 8	/ /	☐	☐	
Day 9	/ /	☐	☐	
Day 10	/ /	☐	☐	
Day 11	/ /	☐	☐	
Day 12	/ /	☐	☐	
Day 13	/ /	☐	☐	
Day 14	/ /	☐	☐	
Day 15	/ /	☐	☐	
Day 16	/ /	☐	☐	
Day 17	/ /	☐	☐	
Day 18	/ /	☐	☐	
Day 19	/ /	☐	☐	
Day 20	/ /	☐	☐	
Day 21	/ /	☐	☐	
Day 22	/ /		☐	
Day 23	/ /		☐	
Day 24	/ /		☐	
Day 25	/ /		☐	
Day 26	/ /		☐	
Day 27	/ /		☐	
Day 28	/ /		☐	

Patient signature: _____ Date: _____/_____/_____

PATIENT MEDICATION DIARY *(Palbociclib + Fulvestrant)*

Study: Phase II Safety Study of Palbociclib with Letrozole or Fulvestrant in African American Women with Hormone Receptor Positive HER2 Negative Advanced Breast Cancer

Subject #: _____ Site: _____

Cycle #:_____ Current dose of palbociclib: _____mg

*Take one Palbociclib capsule with food on Days 1-21. If you miss a day's dose entirely, you should **NOT** make it up the next day. If you inadvertently take 1 extra dose during a day, you should **NOT** take the next day's dose. Unused drug and/or empty bottles should be RETURNED to the site at the next visit. Please record your diary daily. Always bring your completed patient diary to the clinic at EACH study visit.*

	Date taken (mm/dd/yyy)	**Palbociclib**	**Fulvestrant**	**Comments** *(Please use this section to write down explanation for any missed doses)*
Day 1	/ /	☐	☐	
Day 2	/ /	☐		
Day 3	/ /	☐		
Day 4	/ /	☐		
Day 5	/ /	☐		
Day 6	/ /	☐		
Day 7	/ /	☐		
Day 8	/ /	☐		
Day 9	/ /	☐		
Day 10	/ /	☐		
Day 11	/ /	☐		
Day 12	/ /	☐		
Day 13	/ /	☐		
Day 14	/ /	☐		
Day 15	/ /	☐	☐	
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Day 24	/ /			
Day 25	/ /			
Day 26	/ /			
Day 27	/ /			
Day 28	/ /			

Patient signature: _____ Date: _____/_____/_____