Protocol #: *16-052*

Title: PELOPS: Palbociclib and **E**ndocrine therapy for **LO**bular breast cancer **P**reoperative **S**tudy: A randomized phase II study of Palbociclib with endocrine therapy versus endocrine therapy alone for Invasive Lobular Carcinoma and Invasive Ductal Carcinoma

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Agent(s): Palbociclib, [redacted]

Study exempt from IND requirements per 21 CFR 312.2 (b).

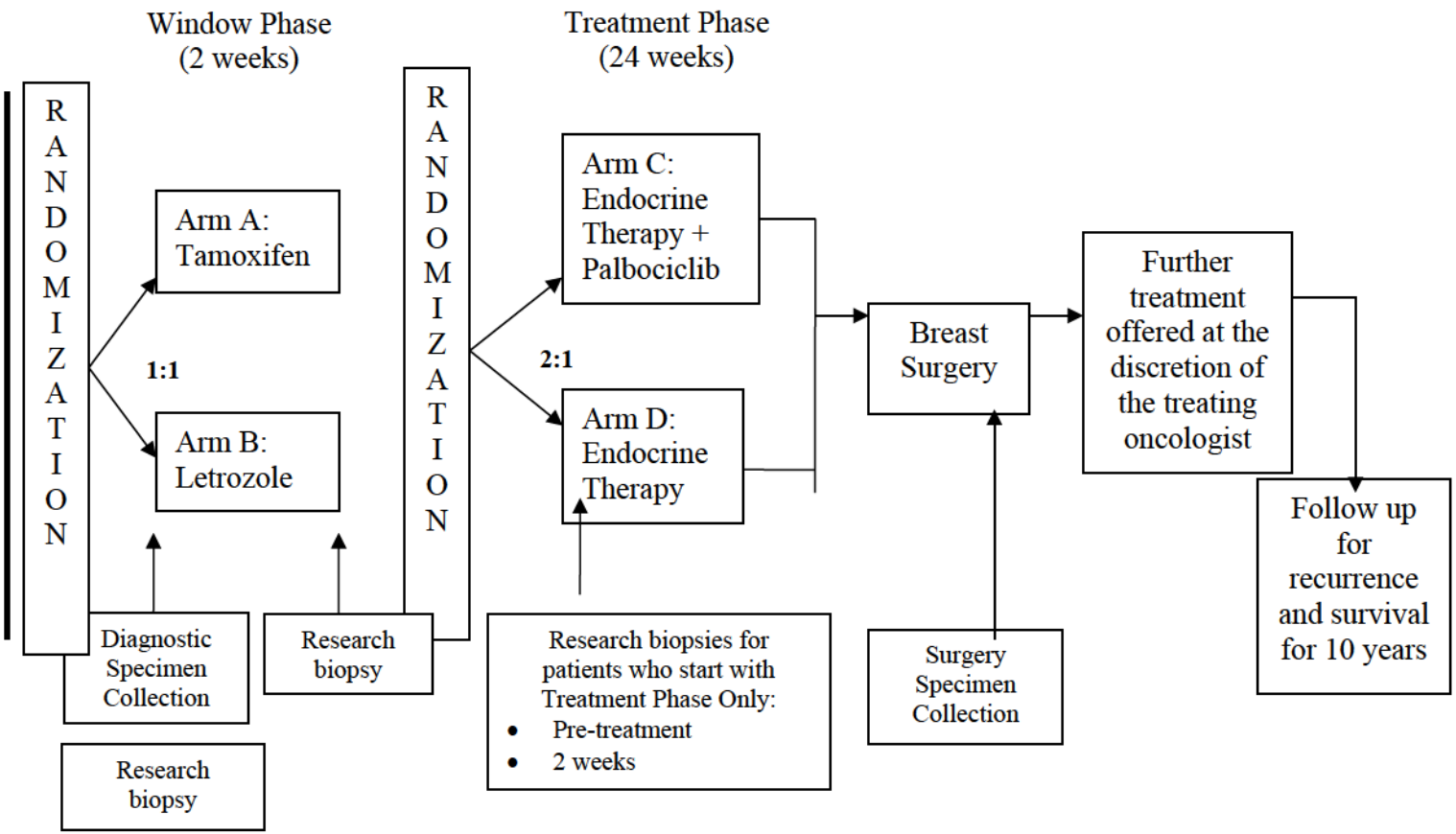
Protocol Type/Version #/Version Date: Sponsor Amendment 8/Version 9/Version date: July 6, 2022

SCHEMA

N=195

Eligibility:

- Tumor size ≥1.5cm
- ER and/or PR-positive, HER2-negative



Stratification Factors

1. Histology: invasive ductal carcinoma vs. Invasive lobular carcinoma
2. Menopausal Status: pre vs. Post menopausal
3. Initial lymph node status: Positive vs. Negative
4. Pre-treatment tumor size: T1-2 vs. T3-T4

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1. OBJECTIVES

1.1 Study Design

This is an open label phase II neoadjuvant clinical trial of Palbociclib in combination with endocrine therapy for ER+ early-stage breast cancer. The planned sample size is up to 195 participants. The study includes a "window of treatment" phase followed by a treatment phase. In the window phase, patients will be treated with a two-week course of tamoxifen (Arm A) or letrozole (Arm B). In the treatment phase participants will be randomized to receive endocrine therapy in combination with palbociclib (Arm C) or endocrine therapy alone (Arm D) for a total duration of 24 weeks.

Study enrollment will be performed as follows: Postmenopausal women diagnosed with either invasive lobular carcinoma (n= 60) or invasive ductal carcinoma (n=60) will be enrolled in the window phase of the study. A research biopsy will be performed before starting and after completing the two-week course of endocrine therapy and patients will continue on study into the treatment phase. Upon completion of enrollment of either the invasive lobular carcinoma or invasive ductal carcinoma subsets in the window phase, the study will be amended such that subsequent postmenopausal patients will be eligible to enroll directly into the treatment phase of the study. Premenopausal patients with either invasive lobular or ductal carcinoma will be eligible to enroll directly into the treatment phase of the study. A research biopsy will be performed before starting and after two weeks of treatment for participants enrolled directly into the treatment phase.

Participants who enroll to the window phase will be randomized for treatment assignment to both study phases at time of registration.

Disease response assessment will be evaluated at baseline and prior to surgery with imaging, and clinically every four weeks during study therapy. Routine imaging is not required during the neoadjuvant treatment, but is recommended for patients not experiencing a clinical response. Definitive breast cancer surgery (excision or mastectomy) marks the end of protocol-mandated therapy. Pathologic response determined by the Residual Cancer Burden calculator will be used for the primary endpoint of this study. The treating oncologist will make decisions regarding choice of post-surgical systemic therapy. However, participants enrolled in this study and randomized to endocrine therapy only will have the option to receive endocrine therapy in combination with palbociclib for a total duration of 6 months in the adjuvant setting.

1.2 Primary Objective

The study has two co-primary objectives:

Window phase: To evaluate the difference in anti-proliferative activity of letrozole versus tamoxifen measured by changes in Ki67 from baseline to research biopsy (day 15) within cohorts of ER+ breast cancer for patients diagnosed with invasive lobular or invasive ductal carcinoma.

Treatment phase: To compare the pathologic response of endocrine therapy plus palbociclib versus

endocrine therapy alone in breast cancer patients diagnosed with hormone receptor positive invasive breast cancer, as determined by the Residual Cancer Burden (RCB)

1.3 Secondary Objectives

- To evaluate the difference in anti-proliferative activity of endocrine therapy plus palbociclib versus endocrine therapy alone measured by changes in Ki67 from baseline to research biopsy (day 15) for premenopausal patients enrolled into the treatment phase of the study.
- To compare the pathologic response of endocrine therapy plus palbociclib versus endocrine therpay alone in breast cancer patients as determined by the modified Preoperative Endocrine Therapy Prognostic Index (mPEPI)
- To determine the clinical response rate, defined as the number of partial and complete responses after preoperative endocrine therapy plus palbociclib and of endocrine therapy alone in breast cancer patients diagnosed with hormone receptor positive invasive breast cancer
- To characterize safety and tolerability of palbociclib given in combination with endocrine therapy in the preoperative setting

1.4 Correlative Science Objectives

- To interrogate differences in the estrogen receptor transcriptional regulation for patients diagnosed with ILC and IDC
- To explore the differences in anti-proliferative activity of letrozole and tamoxifen measured by changes in Ki67 from baseline to research biopsy (day 15) within cohorts of Luminal A (LA) and Luminal (B) invasive breast cancer.
- To explore the correlation of Rb phosphorylation and Ki67 change from baseline to research biopsy (day 15) among patients treated with endocrine therapy plus palbociclib or endocrine therapy alone (i.e. participants enrolled straight into the treatment phase of the study)
- To describe the association between whole exome sequencing and copy number findings and pCR
- To explore whether molecular features of invasive lobular carcinoma predicts for greater sensitivity to palbociclib when compared to invasive ductal carcinoma. Molecular features of ILC include but are not limited to higher frequency of cyclin D1 amplification, and enrichment for Luminal A subtype when compared to IDC.
- To characterize serial changes in immune marker profile in peripheral blood mononuclear cells (PBMCs) among patients treated with endocrine therapy with or without palbociclib
- To explore whether induction of changes in the immunosuppressive and/or immune-stimulating immune marker profile in PBMCs correlates immune marker profile changes in the research biopsies

- To determine whether the Recurrence Score is associated with response to neoadjuvant endocrine therapy.

- To determine whether the SET2,3 index is associated with response to neoadjuvant endocrine therapy.
- To compare rates and patterns of pathologic nodal response among patients treated with endocrine therapy, with or without palbociclib.
- To characterize axillary surgical management based on volume of residual nodal disease following endocrine therapy, with or without palbociclib.
- To determine outcomes based on definitive axillary lymph node surgery performed following endocrine therapy, with or without palbociclib.
-

2. BACKGROUND

2.1 Study Disease(s)

Invasive lobular carcinoma (ILC) is the second most histological subtype of breast cancer accounting for 10-15% of all breast cancer cases [1-3]. ILC differs from invasive ductal carcinoma (IDC) with respect to epidemiology, clinical presentation, histological features, and responsiveness to systemic treatments [4]. At the morphological level, ILC are commonly represented by small cells lacking cohesion and arranged in single file linear cords, and generally classified as hormone receptor positive tumors (ER+), HER2 negative, with low to intermediate histological grade. In a retrospective analysis performed using data from the BIG 1-98 study, patients diagnosed with ILC had inferior outcome when treated with tamoxifen when compared to patients diagnosed with IDC and also treated with tamoxifen. Despite the recognized differences, clinical trials have not considered ILC as a distinct disease subset. The current study includes patients diagnosed with ILC and IDC classified as hormone receptor positive and HER2 negative. The neoadjuvant design will allow us to investigate the differential effectiveness of tamoxifen versus letrozole after a short two-week treatment exposure. The second part of this study will allow us to investigate the efficacy of palbociclib when combined with adjuvant endocrine therapy. Palbociclib is now an approved agent for patients for patients diagnosed with advanced estrogen receptor positive breast cancer. Palbociclib is also being evaluated in combination with endocrine therapy in the PALLAS adjuvant clinical trial.

Agent(s)

The use of Palbociclib and Letrozole in the early-stage setting in the current study follows safety data provided by studies conducted in advanced setting as summarized below.

2.1.1 Palbociclib

PD-0332991 (palbociclib), an orally active pyridopyrimidine, is a potent first-in-class, highly selective reversible inhibitor of CDK4 and CDK6 (IC50 = 11 nM; Ki = 2 nM) with a molecular weight of 447.53. Data from nonclinical studies indicate that palbociclib may have cytoreductive as well as cytostatic effects on tumor cells. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in

laboratory models and in early clinical trials. CDK4 and CDK6 control G1 to S phase transit by binding to D-type cyclins [5-7]. The CDK4/6/Cyclin D1 complex phosphorylates the retinoblastoma susceptibility (*RB1*) gene product (Rb), releasing the E2F and DP transcription factors that drive expression of genes required for S-phase entry. CDK activity and G1 progression is negatively regulated by Cip-Kip (P27,P21) and INK4 family, typified by p16 [8-12]. Overexpression of p16 in cells with normal Rb inhibits both CDK4-and CDK6- associated kinase activity and Rb phosphorylation, with subsequent cell cycle arrest [13, 14].

There is a strong link between the actions of estradiol and the G1-S phase transition, where the estradiol effector is the cyclin D1-CDK4/6-Rb complex [15]. Cyclin D1 is a direct transcriptional target of ER [16, 17] and microinjection of antibodies to cyclin D1 inhibits estrogen-induced S-phase entry. In addition, anti-estrogen-induced growth arrest of ER+ breast cancer cells is accompanied by decreased cyclin D1 expression [18], while endocrine resistance is associated with persistent cyclin D1 expression and Rb phosphorylation [19]. Consistent with the notion that the main function of cyclin D1 is to activate CDK4/6, its oncogenic activity is dependent on CDK4/6-associated kinase activity [20] and CDK4/6 inhibitors are most effective in tumors with gene amplification and overexpression of cyclin D1 [21-23], which is common in ER+ breast cancer. Genetic aberrations leading to hyperactivation of cyclin D1-CDK4/6 is particularly common in ER+ breast cancer [24], consistent with its critical role in the tumorigenesis of this cancer subtype, making CDK4/6 inhibitors particularly attractive agents for ER+ breast cancer.

Palbociclib Preclinical Data

Palbociclib preclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytoreductive activity. Single agent palbociclib has shown antiproliferative effects (selective G_1 arrest) on Rb-positive cancer cells *in vitro* and *in vivo* [22] where palbociclib activity was associated with reduced Rb-phosphorylation and decreased expression of the cell proliferation marker Ki67. Palbociclib showed no activity in Rb-negative tumor cell xenografts, consistent with CDK4/6 inhibition as the sole mode of action [22].

Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific pRb phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of pRb. The IC_{50} values for reduction of pRb phosphorylation at serine -780 and -795 in MDA-MB-435 breast carcinoma cells were 0.066 and 0.063 μM, respectively. The IC_{50} values for reduction of pRb phosphorylation are similar to the IC_{50} values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

Palbociclib was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to palbociclib ($IC_{50} < 150$ nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell lines show the opposite characteristics. In this study, ER+ breast cancer seems to be particularly appropriate for treatment with palbociclib; sensitive cell lines in this panel represent mostly the luminal ER+ subtype [29]. The combination of palbociclib with tamoxifen has been tested in vitro in ER+ breast cancer cell lines indicating a synergistic interaction and provided a biologic rationale for evaluating the combination of palbociclib with anti-hormonal therapy in the clinic.

In nonclinical studies, palbociclib and its active lactam metabolite, PF-05089326, demonstrated little or no inhibition of cytochrome P450 (CYP) 1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 enzyme activities and thus, showed low potential for PK DDI with drugs that are substrates for these CYPs. However, palbociclib and its metabolite, PF-05089326, caused time-dependent inhibition of CYP3A-mediated midazolam 1'-hydroxylase and testosterone 6β-hydroxylase activities and, therefore, may have the potential for PK DDI with drugs for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance. Palbociclib did not cause induction of CYP1A2, CYP2B6, CYP2C8, or CYP3A4 messenger ribonucleic acid expression and/or enzyme activity in vitro in human hepatocytes at concentrations exceeding 50-fold of the palbociclib unbound steady-state plasma C_{max} determined at therapeutic doses in humans; thus, the potential for palbociclib to induce these enzymes is considered to be low at clinically relevant concentrations. The potential for palbociclib to inhibit the activities of selected uridine diphosphate glucuronosyltransferase (UGT) enzymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) was also assessed, and the likelihood of DDI associated with inhibition of these Phase 2 enzymes at clinically relevant concentrations is considered low.

Inhibition of efflux transporters (p-glycoprotein [P-gp] and breast cancer resistant protein [BCRP]), hepatic uptake transporters (organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3), hepatic efflux transporter (bile salt export pump [BSEP]), and renal transporters (organic anion transporter [OAT] 1, OAT3, and organic cation transporter [OCT] 2) by palbociclib was assessed in vitro and was considered to be unlikely at clinically relevant palbociclib concentrations.

In vitro, palbociclib is metabolized mainly by CYP3A and sulfotransferase 2A1 (SULT2A1) enzymes. Drugs that are known to induce or inhibit the activities of these enzymes may alter the clearance and systemic exposure of palbociclib.

Palbociclib Pharmacokinetic (PK) Data

To date, pharmacokinetic data have been collected in 8 clinical studies for a total of over 250 advanced cancer patients and 30 healthy volunteers (A5481001, A5481002, A5481003, A5481004, A5481008, A5481009, A5481010, and A5481011). In the FIP trial (A5481001) the exposure increased in a dose proportional manner over the dose range of 25 to 225 mg QD following palbociclib administration on Days 1 and 8 of Cycle 1, although some variability (low to moderate) around these doses was observed particularly at the 150 mg QD dose level. Following repeated daily dosing to steady state, palbociclib was absorbed with a median T_{max} of ~4 hours. The mean palbociclib Vz/F was 2583 L, which is significantly greater than total body water (42 L), indicating that palbociclib extensively penetrates into peripheral tissues. Palbociclib was eliminated slowly; the mean elimination half-life ($t_{1/2}$) was 28.8 hours and the mean CL/F was 63.1 L/hour. Palbociclib accumulated following repeated dosing with a median R_{ac} of 2.4, which is consistent with the terminal half-life.

The effect of food on the bioavailability of palbociclib when administered as the commercial free base capsule, was investigated in Study A5481021. The administration of the free base formulation of palbociclib with food (including a high fat or a low fat meal given together with palbociclib, or moderate fat meals given 1 hour before and 2 hours after palbociclib) resulted in

more uniform drug absorption and significantly reduced the intersubject variability in drug exposure when compared to the administration of free base formulation of palbociclib in a fasted state. The relative bioavailability of the commercial free base capsule administered with food and the isethionate capsule administered under overnight and minimal fasting conditions was investigated in Study A5481036. The two fasting conditions for administration of isethionate capsules represent the 2 extreme scenarios for compliant palbociclib dosing with regard to food intake in the pivotal Phase 1/2 efficacy trial, Study A5481003, in which patients were instructed to fast from 1 hour before until 2 hours after palbociclib dosing. The administration of palbociclib free base capsule formulation with food was found to be bioequivalent to palbociclib isethionate capsule formulation given under both the overnight and minimal fasting conditions. As a result of these findings, it is recommended that free base formulations of palbociclib be administered with food.

Pharmacokinetic data are available from an itraconazole DDI study where the effect of multiple dosing of a potent CYP3A4 inhibitor, itraconazole (200 mg QD), on the single-dose PK of palbociclib (125 mg) was evaluated in 12 healthy fasted subjects (Study A5481016). Median palbociclib plasma concentrations were higher in the presence of itraconazole than those in the absence of itraconazole. Palbociclib mean plasma AUC from time 0 to infinity (AUC_{inf}) and C_{max} values increased approximately 87% and 34%, respectively, when administered in combination with itraconazole compared to when administered alone. Therefore, concomitant administration of agents known to be strong inhibitors of CYP3A isoenzymes (such as ketoconazole, miconazole, itraconazole, posaconazole, clarithromycin, erythromycin, telithromycin, nefazodone, diltiazem, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, and grapefruit juice) should be avoided.

Pharmacokinetic data are available from a rifampin DDI study where the effect of multiple dosing of a potent CYP3A4 inducer, rifampin (600 mg QD), on the single-dose PK of palbociclib (125 mg) was evaluated in 15 healthy fasted subjects (Study A5481017). Median palbociclib plasma concentrations were substantially lower in the presence of rifampin than those in the absence of rifampin. Palbociclib mean plasma AUC from time 0 to infinity (AUC_{inf}) and C_{max} values decreased approximately 85% and 70%, respectively, when administered in combination with rifampin compared to when administered alone. Therefore, co-administration of palbociclib with strong CYP3A inducers (such as phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, and St. John's Wort) should be avoided.

Palbociclib and PF-05089326 caused time-dependent inhibition of CYP3A in in vitro assays. Pharmacokinetic data are available from a midazolam DDI study where the effect of multiple dosing of palbociclib (125 mg QD) on the single-dose PK of a sensitive CYP3A4/5 probe substrate, oral midazolam (2 mg), was evaluated in 26 healthy women of non-childbearing potential (Study A5481012). When midazolam was administered with palbociclib 125 mg QD at steady-state, the mean midazolam plasma C_{max} and AUC_{inf} values increased approximately 38% and 61%, respectively, as compared with those determined after administration of midazolam alone. These results indicate that palbociclib is a weak time-dependent inhibitor of CYP3A.

Palbociclib Dose Rationale

Palbociclib has been tested in a Phase 1 dose escalation Study (A5481001) in 74 patients with advanced cancer. Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on treatment/1 week off treatment) and Schedule 2/1 (2 weeks on treatment/1 week off treatment). All dose limiting toxicities (DLTs) observed in this study were related to myelosuppression and mainly consisted of Grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, neutropenia was reversible and non-cumulative. The most common non-hematological adverse events included fatigue, anemia, diarrhea, constipation, vomiting and dyspnea, all with mild to moderate severity. A greater proportion of patients on the 2/1 schedule had treatment-related TEAEs during and after Cycle 1 than patients on the 3/1 schedule although the proportion of patients with treatment-related neutropenia was similar with respect to the 2 dosing schedules, both during and after Cycle 1. One partial response (PR) was reported in a patient with testicular cancer. A total of 13/37 patients treated with Schedule 3/1 evaluable for efficacy experienced stable disease (SD), including 6 patients with SD lasting 40 weeks or longer. One of these patients was a woman with ER+ breast cancer who had previously received 7 lines of treatment for her disease. This patient remained on treatment for 80 weeks (7 cycles at 50 mg/d and 13 cycles at 75 mg/d) and eventually discontinued treatment due to disease progression. Based on the relatively improved safety profile of Schedule 3/1, and the efficacy results from this study, the Schedule 3/1 has been selected for further clinical development and the RP2D for this schedule was determined to be 125 mg/day. This schedule and associated RP2D was further explored in combination with letrozole in the Phase I/II study in patients with advanced breast cancer described below.

Palbociclib Clinical Data

A phase II study with single agent palbociclib in 36 women with advanced breast cancer was reported at the American Society of Clinical Oncology (ASCO) 2013 from 28 women who have completed cycle 1 [30]. Palbociclib is given at 125 mg orally, days 1- 21 of a 28-day cycle. Of the 28 women, 18 (64%) women are HR+/HER2-, 2 (7%) are HR+/HER2+ and 8 (29%) HR-/HER2-negative. 90% had prior chemotherapy for metastatic disease (median 3 lines); 78% had prior hormonal therapy (median 2 lines). Grade 3/4 toxicities were limited to transient neutropenia (n=14; 50%) and thrombocytopenia (n=6; 21%). One episode of febrile neutropenia occurred in a patient with six previous chemotherapy regimens. All other toxicities were grade 1/2. Treatment was interrupted in 7 (25%) and dose reduced in 13 (46%) patients for cytopenias; 27/28 patients discontinued study for disease progression. (PR + SD >6 months) was as follows: 4 patients (23%) in HR+/HER2-negative (n=18), 1 (50%) in HR+/HER2+ (n=2), 1 (13%) in HR-negative/HER2-negative (n=8). In conclusion, therapy with palbociclib alone is well-tolerated, and demonstrates clinical benefit in patients with all subtypes of breast cancer and despite progression on prior hormonal- and chemotherapy. Translational studies examining molecular predictors of response are in progress.

A randomized, multicenter active-controlled Phase I/II Study (A5481003) was designed to assess the efficacy, safety and PK of letrozole 2.5 mg QD in combination with palbociclib 125 mg QD (schedule 3/1) versus single agent letrozole 2.5 mg QD for the first-line treatment of ER+/ HER2-negative advanced breast cancer in postmenopausal women. Letrozole was selected as the active control based on its worldwide approval and use as standard of care for the first-line hormonal treatment of postmenopausal women with ER+ advanced breast cancer.

Study A5481003 included a limited Phase I portion, aimed at confirming the safety and tolerability of the combination and excluding a PK interaction with the combination, and a randomized Phase II portion aimed at evaluating the efficacy and safety of letrozole in combination with palbociclib when compared to letrozole alone in the first-line treatment of postmenopausal patients with ER+/HER2-negative advanced breast cancer. The Phase II portion, also called PALOMA-1, consisted of 2 parts [25]. In Part 1, patient selection was based only on ER/HER2 status. In Part 2, patients were prospectively selected also taking into account tumor CCND1 amplification and/or p16 loss. A total of 177 patients were enrolled in the study. Twelve (12) were enrolled in the Phase 1 portion and 165 (66 and 99 in Part 1 and 2, respectively) were enrolled in the Phase 2 portion. Results from the Phase 1 portion indicated no PK interaction between palbociclib and letrozole. The RP2D was determined to be 125 mg QD on Schedule 3/1 (3 weeks continuous treatment followed by 1week off treatment) in combination with letrozole 2.5 mg QD continuously. PRs were reported for 3 (33%) out of 9 patients with measurable disease (3 had bone-only disease). Another 5 patients (42%) had stable disease for ≥ 6 months and the clinical benefit rate (PR + SD ≥ 6 months) was 67%. Eight (8) patients discontinued from the study due to disease progression, including 2 patients with clinical progression, 1 patient withdrew consent, and 3 patients are still ongoing.

Two interim analyses for the Phase 2 portion of the study have been conducted. The results of the interim analyses showed consistent trend of clinically meaningful improvements in PFS (primary endpoint). In the first interim analysis (Part 1; N=66), the median PFS for the palbociclib plus letrozole arm was 18.2 months versus 5.7 months for the letrozole alone arm (HR=0.35; 95% CI: 0.17, 0.72; p=0.006). The second interim analysis (N=165) continued to demonstrate a statistically significant improvement in PFS (26.1 vs. 7.5 months, respectively; HR=0.37; 95% CI: 0.21, 0.63; p <0.001) [25]. More recently, the final analysis demonstrated a statistically significant improvement in PFS for the palbociclib plus letrozole arm (20.2 months) versus the letrozole arm (10.2 months) with hazard ratio (HR=0.488; 95% CI: 0.319, 0.748, p=0.0004). These results indicate that the combination of palbociclib with letrozole is well tolerated with a safety profile similar to that seen with either palbociclib or letrozole when administered alone. The most frequently reported treatment-related adverse events included neutropenia, leukopenia, anemia, and fatigue. There were no cases of febrile neutropenia reported to date in this study. Overall, 8 patients in the combination arm were discontinued from the study treatment due to an adverse event, of which 5 were considered treatment-related (grade 3 neutropenia [n=4] and ischemic colitis) and 1 patient from the letrozole alone arm. Additionally, the combination demonstrated antitumor activity, which was consistent with the sensitivity of ER+ breast cancer observed in the preclinical models.

2.2 Rationale

Invasive lobular carcinoma has unique clinical and biological features but has not been studied as a separate disease subset in prospective clinical trials. In the “window” phase of the study we will investigate the differential effectiveness of tamoxifen versus letrozole for patients diagnosed with invasive lobular carcinoma (ILC) or invasive ductal carcinoma (IDC). In the treatment phase of the study we will investigate the benefit of palbociclib in combination with endocrine therapy in the neoadjuvant setting. We expect that the treatment phase will provide us with relevant insights related to the efficacy of palbociclib in early-stage hormone receptor positive disease. In addition

to the primary clinical objective, we plan to explore the efficacy of palbociclib + letrozole according to pathology defined subtypes (i.e. ILC, IDC) and genomically defined subtypes (i.e. luminal A vs. luminal B). Palbociclib is now under investigation in a large adjuvant phase III study and results from the neoadjuvant setting can be informative for future translational research efforts using samples from a large adjuvant study.

The window phase of the study is built following observations from a retrospective analysis conducted using data from the BIG 1-98 phase III study [26]. BIG 1-98 was a randomized, phase III study that compared five years of tamoxifen or letrozole (monotherapy arms), or their sequences in post-menopausal women with hormone receptor positive early-stage breast cancer. There were 4922 patients enrolled in the monotherapy arms of BIG 1-98. The analysis included patients who had centrally-reviewed histology data and classified as IDC and ILC (n = 3660). In summary the magnitude of benefit of adjuvant letrozole was higher in the ILC subset when compared to IDC. Of interest, and in contrast to IDC, LA ILC derived a significant benefit in favor of letrozole, while LA ILC treated with tamoxifen had the worse disease-free survival. In the LB subset (Fig 2) we observed a significant benefit in favor of letrozole in both subgroups. In the multivariate analyses correcting for classic clinico-pathologic variables we observed a significant benefit in favor of letrozole in the ILC subset for both disease-free survival and overall survival. The findings from the BIG 1-98 strongly suggest that ILC is partially resistant to tamoxifen.

In the window phase of the current study, patients diagnosed with either ILC or IDC will be treated with a 2-week course of tamoxifen or letrozole. The suppression of Ki67 was selected as the primary endpoint for this initial phase of the study following data from previous studies conducted using endocrine therapy in the neoadjuvant setting. In the IMPACT trial, suppression of Ki67 after 2 and 12 weeks was significantly greater with anastrozole than with tamoxifen (P = 0.004). In the P024 trial, treatment-induced reduction in geometric mean Ki67 was significantly greater with 4 months of letrozole (87%) than tamoxifen (75%; analysis of covariance P = 0.0009). In the ACOSOG Z1031 trial, the effects on Ki67 were similar among all three AIs (anastrozole 78%, exemestane 81.2% and letrozole 87.1%). The available data indicates that Ki67 modulation in the neoadjuvant setting can be used as a robust endpoint.

In addition to Ki67, levels of estrogen (ER) and/or progesterone receptor (PgR) expression have also been associated with response to neoadjuvant endocrine therapy. In the IMPACT study there was a positive correlation between ER level and degree of Ki67 suppression at both 2 and 12 weeks. In the same study, a greater suppression of Ki67 was observed in the subset classified as PgR positive versus PgR negative. In addition to single biomarker measurements, the preoperative endocrine prognostic index (PEPI) score was proposed as a combination of markers markers that have been shown to have prognostic utility among patients treated with neoadjuvant endocrine therapy. PEPI score includes residual Ki67 and measures of on-treatment ER, pathological tumor size and nodal status.

In the current study, central assessment of Ki67 at baseline, 2-weeks and at the end of treatment along with measurement of ER and PgR will provide us with robust scientific data to explore the proposed research questions. In addition to established markers the current study will include immunohistochemistry staining for Retinoblastoma (Rb) and phospho-Rb. In a previous study evaluating the efficacy of palbociclib among patients diagnosed with mantle cell lymphoma, the

degree of reduction of phospho-Rb was highly correlated with that of Ki67 (r= 0.91). The design of the current study will allows to investigate the degree of phospho-Rb suppression among patients treated with endocrine therapy plus or minus palbociclib.

2.3 Rationale - Correlative Studies

In the current study we plan to expand upon previous findings and further investigate the molecular underpinnings of invasive lobular carcinoma and invasive ductal carcinoma in the context of a clinical trial. The main objective of PELOPS Translational Research program is to evaluate whether tumor-derived molecular or genomic alterations predict benefit from the proposed treatment interventions. ‘

In the window phase of the study, we will investigate the mechanisms driving the differential the differential effectiveness of endocrine therapies in ILC when compared to IDC tumors. As an initial approach to this question, we plan to perform genome-wide analyses of estrogen receptor (ER)-binding sites (known as the ER cistrome) in ILC and IDC tumor samples treated with a two-week exposure of tamoxifen or letrozole. We hypothesize that epigenetic features of ILC (ER-binding and/or enhancer changes) will provide us with hypothesis related to the differential effectiveness of endocrine therapies for patients diagnosed with ILC or IDC.

The identification of ER-binding sites or cistrome was initially performed in IDC cell lines using chromatin immunoprecipitation (ChIP) coupled with massively parallel sequencing (ChIP-seq) [27]. So far, the most significant findings with Chip-seq experiments in cell lines can be summarized as: 1) ER frequently binds distal enhancers [27], 2) the forkhead protein FoxA1 is necessary for ER-chromatin interactions [28, 29] and 3) activation of growth factor receptor signaling results in the redirection of ER binding [30]. Ross-Innes and colleagues performed ER ChIP-seq experiments in 15 ER+ tumors (eight with a good prognosis and seven with a poor prognosis) and three distant metastases [31]. Despite small numbers the study suggested differential ER binding sites is associated with the outcome of patients with breast cancer. Moreover, an interesting finding of this study was that ER is still bound to DNA in tumors resistant to hormonal therapies but was recruited to novel sites in the genome. These sites are functionally and biologically relevant since a gene expression predictor based on genes within a 20-kb window of the binding sites was associated with survival in ER+ datasets.

In addition to CISTROME related questions, we will investigate tumor features using tumor-derived DNA, RNA and protein expression for genetic and molecular discovery.

RNA-sequencing (RNA-seq) technology will be used to define the so-called intrinsic breast cancer subtypes. The definition of LA and LB subtypes will be defined using pre-established classifiers. In a retrospective series [32] including 166 ILC tumors profiled by Affymetrix, the proliferation-based gene signature Genomic Grade Index (GGI) provided us with relevant information showing that a significant fraction of ILC is classified as high risk by GGI. We subsequently classified the subset of ILC according to the PAM50 classifier [33]. ILC tumors were mainly characterized as luminal A (LA), (76%, n=133) and luminal B (LB), (20%, n=34) followed by a minority of HER2-positive (2%, n=3), basal (1%, n=2) and normal-like (1%, n=2). In the current study we plan to investigate the efficacy of palbociclib in the LA and LB subtypes.

DNA-based sequencing assays have described the so-called "somatic landscape of genomic alterations" for early-stage ILC, but there is limited information linking "genomic scars" and treatment benefit. In the current study we plan to sequence tumors using either targeted sequencing approach or more comprehensive approaches (e.g. whole genome or whole exome) and interrogate whether "patterns" of somatic alterations predict benefit to treatment.

Preliminary results from sequencing studies and data from publicly available repositories indicate that ILC tumors have a different genomic architecture when compared to IDC tumors. In an early report, Shah et al. [34] described the genomic architecture of a primary ILC tumor with its paired metastatic tumor sample (pleural effusion) obtained 9 years after the primary diagnosis. In this analysis, out of 32 somatic alterations found in the metastatic site, only 11 were found in the primary tumor providing insights into the natural history of disease progression. Subsequently, a cohort of 192 additional tumors (112 ILC and 80 ductal) was screened for somatic mutations in nine of these genes: *PALB2, USP28, HAUS3, KIAA1468* (found in the primary tumor and metastasis), *ERBB2, CDC6, CHD3, SP1, DLG4* (metastasis-specific mutations). Only two genes were found to be mutated in this cohort; *ERBB2* mutations were identified in 3 cases (2 ILC, 1 IDC) and *HAUS3* mutations were detected in 2 ILC cases. Initial data from the Cancer Genome Atlas (TCGA) [35], showed mutations in the gene encoding e-cadherin (CDH1) in 30 out of 36 samples; and 4 of 8 somatic variants in HER2 were found in ILC cases with three of this mutations present within the tyrosine kinase domain. More recently, data from two retrospective series provided significant information related to the somatic landscape of invasive lobular carcinoma. The largest series (Desmedt, Metzger et al. JCO in press) include 630 ILC tumors. Our investigations included high-throughput sequencing of 360 cancer-related genes; genome-wide copy number aberration detection, as well as the assessment of downstream transcriptome. The novel and relevant findings are summarized as follows: 1) 5.1% incidence of HER2 mutations, 3.6% of HER3 mutations with a suggestion of inferior survival outcome among those classified as HER2-mutant. 2) Copy number gains of chromosome 6q25.1, which encompasses ESR1was seen in 25% of cases. Of importance, ESR1 gains were associated with increased ESR1 mRNA along with increased expression of ESR1-target gene TFF1 pointing towards a functional role for this alteration in lobular breast cancer. 3) Alterations in key genes related to PIK3CA signaling were present in 50% of patients. PIK3CA gene mutations were associated with low proliferation defined by Ki67. AKT mutation was present in 4% of patients with a suggestion of inferior survival outcome in this subset. In an elegant work recently presented by the TCGA network [36] a total of 817 breast tumors, including 127 ILC, 490 ductal, and 88 mixed IDC/ILC were profiled. In addition to e-cadherin loss, mutations targeting PTEN, TBX3 and FOXA1 were enriched in the ILC subset. PTEN loss was associated with increased AKT phosphorylation. Importantly, the comprehensive TCGA work suggested that proliferation and immune-related signatures determined three ILC transcriptional subtypes associated with survival differences. Mixed IDC/ILC cases were molecularly classified as ILC-like and IDC-like revealing no true hybrid features.

RNA- and DNA-based sequencing assays will be complement by classic pathology when necessary. Markers associated with benefit and/or resistance to palbociclib will include but may not be limited to genes, proteins, and RNAs relevant to the cell cycle (e.g., CCND1 amplification, CDKN2A deletion), drug targets (e.g., CDK 4/6), and tumor sensitivity and/or resistance (cyclin E, PI3K, p16). Ki67, Rb, phospho-RB, estrogen receptor and progesterone receptor will be

centrally evaluated at the Brigham and Women's Pathology core.

The current study also includes a discovery assay dedicated to understand the efficacy of palbociclib at a cellular level. As part of an investigational protocol conducted at the DFCI, research biopsies will be stained with multiple markers (approx. 20 markers) simultaneously with an aim to investigate whether palbociclib changes the cellular composition of the tumor.

In addition to the above-mentioned assays, the current protocol will investigate whether molecular alterations found in tumor biopsies are detectable in peripheral circulation. The field of "liquid biopsies" is evolving quickly and we expect to use the most updated sequencing approach to study the collected samples. Samples will be processed for cfDNA and germline DNA.

SET Index Sub-study:

Prognostic genomic signatures applied to FFPE samples have become standard tests for patients with Stage I breast cancer, but their absolute prognostic estimates in clinical Stage II-III disease are less compelling [37-40]. This raises the corollary of whether a quantitative scale of predicted sensitivity to endocrine therapy (SET) would inform the selection of optimal candidates for neoadjuvant endocrine-based treatment and which endocrine approach to propose. Expression level of ER transcript (ESR1) is bimodally distributed in breast cancers, corresponding to ER IHC status [41, 42] However, measurement of ESR1 expression level has only modest ability to predict endocrine treatment benefit [43].

The SET2,3 Index was designed to measure the $SET_{ER/PR}$ index of transcription correlated with the expression of both estrogen and progesterone receptors (but not proliferation), and adjusted for a baseline prognostic index (BPI) based on clinical tumor and nodal status at time of diagnosis and a 4-gene classifier (RNA4) - a simple subtype classifier based on the expression of *ESR1*, *PGR*, *ERBB2* and *AURKA* (Du *et al*, manuscript in preparation) [44-47]. Thus, SET2,3 index is the weighted sum of BPI index and the $SET_{ER/PR}$ index. The $SET_{ER/PR}$ Index represents an improvement on the published SET index of ER-related gene expression in breast cancer[47]. It is calculated as the difference in the means of expression between the 18 informative genes and 10 reference genes.

The $SET_{ER/PR}$ index was measured from a pre-treatment needle biopsy and compared with pathologic response and survival following neoadjuvant chemotherapy (taxane-anthracycline regimens) followed by adjuvant hormonal therapy in two large studies – a 300-patient cohort from MDACC and a 220-patient cohort from the I-SPY2 trial. Note that all patients in these studies had high-risk 70-gene prognostic score (MammaPrint test in the I-SPY2 trial) and 90% of the MDACC cohort had 21-gene recurrence score above 31 (microarray estimate). The 21-gene signature has not been evaluated in the I-SPY2 trial.

In both studies, approximately 40% had high SET2,3 (index $\geq$1.77) and their survival was excellent irrespective of the residual cancer burden (RCB) after neoadjuvant chemotherapy. On the other hand, approximately 60% in both studies had low SET2,3 index, and the prognostic relationship of RCB classes was equivalent to that reported for ER-negative cancer. From this, it seems that patients with high SET2,3 index could represent a population to be offered a neoadjuvant endocrine-based treatment, since response to chemotherapy would be uninformative, and their response to endocrine treatment might guide subsequent adjuvant treatment plans. This population might have improved outcomes from neoadjuvant endocrine

therapy, and this could be tested in the current trial.

The SET2,3 index is measured from FFPE tumor sections, without need for RNA extraction, and is measured using a bead-based laser detection technology that is widespread in proteomic clinical testing (Luminex, Austin, TX) with Quantigene Plex (QGP) oligonucleotide detection and labeling (ThermoFisher, Waltham, MA).

Oncotype Dx sub study

The purpose of this sub-study is to explore the use of the Oncotype Dx Recurrence Score in patients enrolled onto a contemporary neoadjuvant endocrine therapy (NET) trial, PELOPS. The risk stratification of estrogen receptor (ER)-positive breast cancers has greatly improved in recent years with the widespread adoption of gene expression profile (GEP) assays in clinical practice. Such tests have therefore become a fundamental component of prognostic assessment and treatment guidelines, serving to assist in decisions about the benefit of chemotherapy in particular [48] Using the *21-gene Breast Recurrence Score*, the Trial Assigning Individualized Options for Treatment (TAILORx) observed a very low distant recurrence rate among women with a Recurrence Score result <11 and demonstrated no benefit from the addition of adjuvant chemotherapy to endocrine therapy for women with an intermediate score of 11-25 [37] Among the 9,719 women included in the trial, 86% had a score ≤25 and thus could potentially be spared adjuvant chemotherapy. Notably, in a sub-analysis, chemotherapy benefit varied by Recurrence Score results among women age <50 years, with possible benefit seen among women with scores between 16-20 and 21-25 [49].

Although the 21-gene assay was validated in the adjuvant setting, it may also be requested upon initial diagnosis to facilitate chemotherapy decision making prior to surgery. In a recent analysis from the National Cancer Database (NCDB), Recurrence Score result reporting among patients undergoing neoadjuvant chemotherapy (NCT) increased from 4.9% to 8.2% between 2010-2015 [49]. In this setting, there is value for the ability of a test to predict response to neoadjuvant therapy in order to facilitate surgery, in addition to the impact of chemotherapy on long-term outcomes.

Comparisons of the 21-gene assay between surgical and core biopsy specimens in breast cancer patients are limited though seem to be clinically acceptable. Several studies in postmenopausal women have shown a correlation between Recurrence Score (RS) < 18 and greater likelihood of response to NET ranging from 59-64% compared to 20-31% for RS ≥ 31 [50-52]. Conversely pathologic response rates to chemotherapy seem to be decreased in patients with low RS [53-55]. In an NCDB analysis of 989 ER+/HER2- patients with available RS undergoing NCT, 4.3% achieved a pCR with the rate increasing to 9.6% in RS ≥ 31[13]. Oncotype RS was prospectively used to guide neoadjuvant systemic therapy decisions and facilitate BCS in a prospective multi-center pilot study[14]. Among 64 non-BCS eligible women, BCS rates were 75% in RS<11 and 72% for RS 11-25 after NET, compared to 64% for RS 11 – 25 and 57% for RS > 25 after NCT. Notably clinical response rates (ultrasound or physical examination) among women with RS 11-25 were significantly higher with NCT vs NET (72.7% vs 50.0%).

In this sub study we will investigate the association between pre-treatment RS and response to NET with or without concomitant CDK4/6 inhibition. Notably, the PELOPS trial includes a significant sub-population (n=45) of premenopausal patients. Premenopausal women have been excluded from most previous studies of NET. This approach has been historically disregarded in this population due to concerns regarding the efficacy of pharmacologic ovarian

function suppression (OFS) and the assumption that chemotherapy is indicated in most premenopausal women with tumors extensive enough to benefit from preoperative downstaging. While professional guidelines, like NCCN, do not directly advocate against this approach, it is generally considered experimental[15, 16]. An association between RS and response to NET among premenopausal would be important for the promotion of this approach among young women in need of neoadjuvant therapy with low likelihood of benefiting from NCT.

Axillary Lymph Node surgery sub study background

There is minimal data regarding axillary lymph node response and lymph node surgery after neoadjuvant endocrine therapy. Most clinical trials to date have reported in-breast tumor response and breast conservation rates. As a result, the National Comprehensive Cancer Network guidelines lack any axillary lymph node surgery guidelines for patients treated with neoadjuvant endocrine therapy. Instead, these patients are grouped with neoadjuvant chemotherapy patients, but the axillary strategies used after chemotherapy, whether it be axillary lymph node dissection or axillary radiation, may be overtreatment in the endocrine-treated population. Surgeons are subsequently left to make axillary surgery decisions following endocrine therapy based on little data and treatments vary widely, including increased performance of axillary lymph node dissection[63], which is a morbid procedure that both patients and providers would like to avoid.

Preliminary, hypothesis-generating work from our group has revealed that the prognostic significance of residual nodal disease after neoadjuvant endocrine therapy is equivalent to that of nodal disease discovered in the upfront surgery population. The NCDB was queried for cT1-3N0-1 HR-positive breast cancer patients treated with neoadjuvant endocrine therapy and axillary surgery between 2010 and 2016. The presence of small volume residual disease after neoadjuvant endocrine therapy (ypN0, ypN0[i+], and ypN1mi) had no effect on 5-year adjusted OS, similar to historic studies in the upfront surgery population[64]. OS was impacted by the presence of residual macrometastatic disease (ypN1) following neoadjuvant endocrine therapy. In a propensity matched analysis, 5-year OS was similar between patients selected for neoadjuvant endocrine therapy and those proceeding to upfront surgery and found to have low volume nodal disease[65].

We then investigated the volumes of residual nodal disease and impact of axillary surgery among stage I-III HR-positive breast cancer patients who were treated with neoadjuvant endocrine therapy in our prospectively-maintained single-institution database (December 2015 – September 2018; N=95) and the NCDB (2012 – 2016; N=3,640). Of the cN0 patients who underwent axillary surgery, most patients had a low volume of residual nodal disease (defined as < 3 positive nodes): 96% (44/46) in the institutional cohort and 91% (2,945/3,227) in the NCDB cohort. In the NCDB cohort[66] there was no difference in 5-year estimated OS by type of axillary surgery (sentinel lymph node biopsy vs axillary lymph node dissection) in any residual nodal disease burden subgroup. These data suggest that most cN0 patients selected for neoadjuvant endocrine therapy have a low residual nodal disease burden and choice of axillary surgery may not impact survival, just as in upfront surgery patients[67].

In summary, these findings suggest that patients treated with endocrine therapy may be safely managed with axillary lymph node surgery strategies resembling those established for patients treated with upfront surgery, instead of those for patients treated with neoadjuvant chemotherapy. We believe that there is an opportunity to de-escalate axillary surgery and the performance of axillary lymph node dissection in patients who are treated with endocrine therapy, but we are in critical need of high-quality axillary nodal response and management data

following endocrine therapy. This trial can provide such data. In this exploratory substudy, we will 1) examine the pathologic response of nodal disease to endocrine therapy +/- palbociclib, and correlate response to Ki67 levels which were obtained for the primary endpoint; 2) characterize the axillary surgical management of the patients treated on PELOPS by both descriptive and mixed-methods analyses; and 3) compare outcomes of axillary surgery (sentinel lymph node biopsy vs axillary lymph node dissection).

3. PARTICIPANT SELECTION

Baseline evaluations (laboratory tests and other non-laboratory tests) must be performed within 28 days of study entry with the exception of the following tests: Documentation of MRI, mammogram, or ultrasound (including DCIS and invasive cancer) of the diseased breast performed within 42 days prior to registration. Mammogram for the unaffected contralateral breast is required within 12 months prior to registration. Serum or urine pregnancy test must be negative in women judged premenopausal within 7 days of randomization, or in women with amenorrhea of less than 12 months at time of randomization (see criteria below).

3.1 Eligibility Criteria

3.1.1 Patients must have Stage I to III histologically confirmed invasive carcinoma of the breast. A minimum tumor size of at least 1.5 cm determined by physical exam or imaging (whichever is larger) is required

3.1.2 Patients must have histologically confirmed hormone receptor positive (ER and/or PR), HER2 negative, early invasive breast cancer. ER, PR and HER2 measurements should be performed according to institutional guidelines, in a CLIA-approved setting in the US or certified laboratories for Non-US regions. Cut-off values for positive/negative staining should be in accordance with current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines. Central confirmation is not required for ER, PR, or HER statuses.

3.1.3 Patients with equivocal HER2 in situ hybridization results according to current ASCO/CAP guidelines are allowed, as long as the clinician has determined that they should be treated as HER2 negative.

3.1.4 For the window phase: Patients must have histologically confirmed invasive lobular carcinoma or invasive ductal carcinoma. No central confirmation of histological subtype is necessary for enrollment. Patients with mixed invasive ductal and lobular carcinoma are eligible and will be stratified as ductal.

3.1.5 For the treatment phase: Patients with any histological subtype are eligible. Patients must be eligible according to the criteria in 3.1.1 and 3.1.2.

3.1.6 Women ≥ 18 years of age. Men are not eligible.

3.1.7 ECOG performance status 0 or 1

3.1.8 Required laboratory values:

- Absolute neutrophil count ≥ 1,500/mm3
- Platelets ≥ 100,000/mm3
- Hemoglobin ≥ 10g/dL
- Total serum bilirubin ≤ ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert's Syndrome
- Aspartate amino transferase (AST or SGOT) and alanine amino transferase (ALT or SGPT) ≤ 2.0 × institutional ULN
- Serum creatinine below institutional upper limit of normal or creatinine clearance ≥ 60 mL/min/1.73 m2 for patients with serum creatinine levels above institutional ULN.

3.1.9 Postmenopausal is defined either by Age ≥ 60, Prior bilateral oophorectomy, or age < 60 with intact uterus and no spontaneous menses over 12 consecutive months. FSH and LH will not be utilized to define menopausal status, unless history of prior total hysterectomy. Premenopausal patients are eligible to participate. Medication-induced amenorrhea will not categorize a patient as post-menopausal; these patients should be treated as pre-menopausal. Premenopausal and peri-menopausal patients should receive ongoing treatment with LHRH agonists (goserolin or leuprolide). Premenopausal patients must be enrolled directly into the treatment phase of the study.

3.1.10 Patient must agree to the required research biopsies at baseline and after the two-week treatment with endocrine therapy in the initial part of the study ("window phase"); or at baseline and after two-week treated with endocrine therapy plus or minus palbociclib for those patients enrolled directly into the treatment phase of the study.

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

3.1.12 Breast imaging should include imaging of the ipsilateral axilla. For subjects with a clinically negative axilla, a sentinel lymph node biopsy will be performed either before or after preoperative therapy at the discretion of the subject's physicians. For subjects with a clinically positive axilla, a needle aspiration, core biopsy or SLN procedure will be performed to determine the presence of metastatic disease in the lymph nodes

3.1.13 Patients with multifocal or multi-centric disease are eligible if the treating clinician has determined the patient should be treated as ER+ and HER2- negative.

3.1.14 Bilateral breast cancers are allowed if the treating clinician has determined the patient should be treated as ER+ and HER2- negative.

3.1.15 Serum or urine pregnancy test must be negative in women judged premenopausal within 7 days of randomization, or in women with amenorrhea of less than 12 months at time of randomization. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation.

3.1.16 Premenopausal patients must agree to use adequate contraception for the duration of protocol treatment and for 6 months after the last treatment with palbociclib. Adequate contraception is defined as one highly effective form (i.e. abstinence, male or female sterilization) OR two effective forms (e.g. non-hormonal IUD and condom/occlusive cap with spermicidal foam / gel / film / cream/ suppository). Hormonal contraceptive methods are not allowed. Patients with hormonal IUD in place are eligible provided the hormonal IUD is removed or replaced by a non-hormonal IUD prior to treatment initiation.

3.1.17 Patients with a history of ipsilateral or contralateral DCIS are eligible.

3.1.18 Patients may concurrently receive bisphosphonates or rank ligand inhibitors while on this study if necessary for treatment or prevention of osteopenia or osteoporosis. Prior treatment with LHRH agonists is allowed for premenopausal women. Topical vaginal estrogen therapy is allowable.

3.1.19 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Concurrent therapy with other Investigational Products.

3.2.2 Prior therapy with any CDK inhibitor.

3.2.3 Patients with Stage IV breast cancer are not eligible. Baseline staging to document absence of metastatic disease is not required, however is recommended as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms). If performed, reports of these examinations must be available. Examination type for staging, i.e. X-ray, sonography, bone scans, CT, MRI, and/or PET-CT, is at the discretion of the investigator.

3.2.4 History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib.

3.2.5 Patients receiving any medications or substances that are potent inhibitors or inducers of CYP3A isoenzymes within 7 days of randomization (see Section 5.11) for list of CYP3A inhibitors and inducers.

3.2.6 Uncontrolled illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, or psychiatric illness/social situations that would limit compliance with study requirements. Ability to comply with study requirements is to be assessed by each investigator at the time of screening for study participation.

3.2.7 Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to randomization, irrespective of the method of contraception used, are excluded from this study because the effect of palbociclib on a developing fetus is unknown. Breastfeeding must be discontinued prior to study entry.

3.2.8 Patients with a history of malignancy are ineligible except for the following circumstances:

- Patients with a history of invasive breast cancer are eligible if they have been disease-free for a minimum of five years
- Patients with a malignancy history other than invasive breast cancer are eligible if they have no active malignancy and are deemed by the investigator to be at low risk for recurrence of that malignancy.
- Patients with the following cancers are eligible: ductal carcinoma in situ of the breast, cervical cancer in situ, and non-metastatic non-melanomatous skin cancers.

3.2.9 Patients on combination antiretroviral therapy, i.e. those who are HIV-positive, are ineligible because of the potential for pharmacokinetic interactions or increased immunosuppression with palbociclib. HIV testing is not required, but patients must not be known to be HIV-positive.

3.2.10 Patients receiving concurrent exogenous hormone therapy (hormone replacement therapy, oral or any other hormonal contraceptives such as hormonal contraceptive coil are not eligible.

3.2.11 Patients are not eligible if they have previously received continuous endocrine therapy (> 30 days) within 5 years prior to diagnosis of the current malignancy. This includes use for prophylactic reasons, including treatment of osteoporosis or cancer prevention with tamoxifen, raloxifene, or AI.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager. All sites should email the documentation listed in section 4.4 to the Project Manager to verify slot availability.

Following registration, participants must begin protocol treatment within 7 business days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled. The Project Manager should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the research nurse or study coordinator should fax or and email the following documentation to [redacted]:

- Clinic visit note documenting history and physical exam
- Pathology report and documentation of ER/PR, and HER2 status
- Email or fax request and confirmation of availability of diagnostic tumor tissue
- Breast imaging report (MRI, Mammogram and/or Ultrasound report)
- CT (chest/abdomen/pelvis) scan report for patients with Stage III disease (if applicable)
- Required laboratory test results including: Hematology (CBC with differential), serum chemistries (creatinine and/or creatinine clearance, bilirubin, ALT, and AST)
- Signed participant consent form
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

To complete the registration process, the Project Manager will

- follow the DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol
- call or email the research nurse or data manager at the participating site with the participant study number, and to confirm registration

NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Project Manager.

5. STUDY PROCEDURES

At the time of registration, the eligibility checklist and supporting documentation to verify eligibility must be provided prior to enrollment. Data will be collected and maintained on study specific case report forms. See Section 10 Study Calendar for additional details.

Patients will be assessed for safety, efficacy and biomarker during the study. All patients will be closely monitored for safety and tolerability during study treatment. Patients should be assessed for toxicity prior to each cycle; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

5.1 Procedures for assigning patients into the study

The study includes a "window of treatment" phase followed by a treatment phase. Patients will be randomized to treatment assignment for each phase at time of registration. In the window phase, patients will be randomized in a 1:1 ratio to receive a two-week course of tamoxifen or letrozole. In the treatment phase participants will be randomized in a 2:1 ratio to receive endocrine therapy in combination with palbociclib or endocrine therapy alone for a total duration of 24 weeks.

Study enrollment will be performed as follows:
Postmenopausal women diagnosed with either invasive lobular carcinoma (n= 60) or invasive ductal carcinoma (n=60) will be enrolled in the window phase of the study. A research biopsy will be performed before starting and after completing the two-week course of endocrine therapy and patients will continue on study into the treatment phase. Upon completion of enrollment of either the invasive lobular carcinoma or invasive ductal carcinoma subsets in the window phase, the study will be amended such that subsequent postmenopausal patients will be eligible to enroll directly into the treatment phase of the study.
Postmenopausal patients randomized to receive letrozole in the window phase may receive continuous letrozole dosing without break between the window and treatment phase.
Premenopausal patients will be eligible to enroll directly into the treatment phase of the study. A research biopsy will be performed before starting and after two weeks of treatment for participants enrolled directly into the treatment phase.

Premenopausal and postmenopausal women will be eligible to enroll in the treatment phase of the study regardless of histological subtype provided that tumors are classified as hormone receptor positive and HER2-negative as specified in 3.1.1 and 3.1.2.

5.2 Medical History and Demographic Data

Medical history includes past or current clinically significant conditions, surgeries, breast cancer surgery and diagnosis, reproductive status, and all medications (e.g., prescription drugs, over the counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to randomization. Demographic data will include age, sex, and self-reported race/ethnicity.

5.3 Physical Examinations

At the initial visit physical examination should include height and weight, breast and local-regional lymphatics. Clinical T and N staging should be documented. At subsequent visits (or as clinically indicated), breast examination and evaluation of local-regional lymphatics should be performed Additional physical examinations should be focused on organ systems related to adverse events. Weight is to be measured on Day 1 of the specified cycles and compared with baseline. Changes from baseline abnormalities should be recorded in patient notes.

5.4 Vital signs

Vital signs will include measurements of pulse rate, and systolic and diastolic blood pressures as well as temperature.

5.5 Laboratory assessments

Samples for the following laboratory tests will be according to the Study Calendar:

Hematology

Hemoglobin, hematocrit, platelet count, WBC count, and differential including absolute neutrophil count

Serum chemistry

Sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, TBILI (and direct bilirubin when TBILI >ULN), ALT, AST, and ALP

Pregnancy test

Serum or urine pregnancy test must be negative in women judged premenopausal within 7 days of randomization, or in women with amenorrhea of less than 12 months at time of randomization. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

5.6 Tumor Staging

5.6.1 Breast and locoregional nodes

All subjects are required to have a MRI, mammogram, or ultrasound performed within 42 days prior to registration. Mammogram for the unaffected contralateral breast is required within 12 months prior to registration. Breast imaging should include imaging of the ipsilateral axilla. For subjects with a clinically negative axilla, a sentinel lymph node biopsy will be performed either before or after preoperative therapy at the discretion of the subject's physicians. For subjects with a clinically positive axilla, a needle aspiration, core biopsy or SLN procedure will be performed to determine the presence of metastatic disease in the lymph nodes. Imaging of the axilla and/or FNA can be performed prior to registration or during the screening phase of the study.

5.6.2 CT scans

It is recommended that subjects with Stage III disease have CT scans of chest, abdomen and pelvis and/or bone scans performed during screening to rule out metastatic disease.

5.7 Surgical Assessment

All subjects will be seen and examined by the treating surgeon at Screening and at the Pre-Operative Visit. Each visit will include a clinical breast and lymph node examination and review of the imaging studies (mammogram, MRI, and any other radiographic method) of the breast and axilla. After examining the subject and reviewing the pertinent radiographic studies at the Screening visit, the surgeon will determine whether the subject is a candidate for potentially curative surgery. At both the Screening and Pre-Operative visits, the surgeon will also determine whether subject is eligible for breast conservation surgery. If the subject is not a breast conservation candidate, the reason(s) will be documented in the CRF (multicentric tumor, tumor location, tumor size, other).

5.8 Tumor Tissue Collection

5.8.1 Diagnostic tissue

A block or minimum of 6 unstained slides from the diagnostic biopsy will be collected at baseline for analysis of Ki67 and additional tests as part of the correlative science plan. Participating sites should confirm availability of archival tissue for correlative analysis prior to registration. This tissue must be sent to the coordinator center after randomization when subject number is assigned; shipping details are provided below in section 5.8.4.

5.8.2 Image-guided research biopsy

Research breast core biopsies of the target lesion will be obtained from all participants at baseline and after a 2-week "window" of endocrine therapy with either tamoxifen or

letrozole. For patients enrolled directly into the treatment phase of the study, the research core biopsies will be performed at baseline and after a 2-week treatment period with either endocrine therapy alone or endocrine therapy in combination with palbociclib. The biopsies represent an integrated assay that will be used in evaluating the primary objective of this study, thus justifying their mandatory collection.

It is strongly recommended that core biopsies be image-guided. The required biopsies include two to three core biopsies placed in 10% buffered formalin (a single pre-filled formalin container is provided in the kit to hold both cores) and two to three core biopsies frozen immediately at bedside in separate OCT blocks to preserve the proteome and transcriptome of the tumor. Biopsy clips are not required, but are permitted, per institutional guidelines.

In a limited subset of participants enrolled at Dana-Farber, 1 core of the research biopsy will be transferred to DMSO as opposed to OCT.

The preferred order of collection is as follows:
Core 1 Formalin
Core 2 Formalin
Core 3 OCT
Core 4 OCT
Core 5 Formalin
Core 6 OCT

Research biopsy kits will be provided by the study. Kits may be ordered from Core Prognostex. Specimens should be shipped per the guidelines in Section 5.8.5. It is anticipated that some patients will be hesitant about completing the research biopsies. Therefore, up to 10 % may opt out one of the research biopsies with prior approval from the overall Principal Investigator. Documentation of this approval must be received prior to registration. This event will not be considered an eligibility exception or major deviation.

5.8.3 Post-surgical tumor sampling

Formalin-fixed Paraffin Embedded Tumor Blocks

The specimen may be blocked using regular cassettes or large cassettes. After the histological assessment of pathologic complete response, blocks should be selected for submission according to the following criteria:

- In case of pCR: submit the block(s) relative to the area(s) closest to the biopsy(ies) site or to the clip if clips are used at the time of biopsy
- In case of residual tumor: submit the block(s) relative to the area(s) close to the clip to previous biopsy(ies). If these block(s) do not include (or only include a minimal portion of) residual tumor, then submit an additional block representative of the main tumor residue.

If institutional policy prohibits the release of blocks, slides can be submitted in place of the block. Submit a minimum of 10 slides relative to the area(s) with the clip or close to biopsy (ies) site.

For patients whose lymph node status at baseline is cN0-3 but is ypN1-3 at surgery, 1 block or 10 unstained slides (5um) will be submitted (containing residual axillary lymph node tumor tissue.) For patients whose lymph node status at baseline is cN1-3 but is ypN0 at surgery, 1 block or 10 unstained slides (5um) will be submitted (ideally containing tumor bed from the axilla or tissue showing treatment effect in the axilla).

5.8.4 Block and Slide Shipping and Storage

Tissue blocks or slides (from both diagnostic biopsy and surgery) should be shipped along with a de-identified pathology report and the Specimen Requisition Form (Appendix B) to Dana-Farber. All samples should be de-identified and labeled with the Participant initials, Participant Study ID number and date of procedure. Tissue material should be sent to the coordinating center at:

[redacted]

Please email the DFCI study BOC translational team at [redacted] mailto:with the sample information and tracking information before shipping archival tissue specimens. The coordinating center will maintain a specimen tracking log of all archival tissue specimens received.

Tumor blocks and slides will be kept for future research at DF/HCC; however, if a tumor block or slides are needed for clinical care purposes, the participating site should contact the coordinating center study coordinator to request that the applicable tissue be returned.

5.8.5 Research biopsy shipping and storage

All biopsy samples should be shipped Monday – Thursday to:

Ashka Patel
Brigham and Women's Hospital
Breast Tissue/Blood Bank
Thorn Building - Room 428
20 Shattuck Street
Boston, MA 02115

OCT specimens should be shipped frozen on dry ice. Formalin should be at room temperature and shipped at ambient temperature.

If a biopsy must be performed on Friday, the specimens should be stored over the weekend and shipped on Monday.

All samples should be de-identified and labeled with the Participant initials, Participant Study ID number and date of procedure. Please email the DFCI study coordinator with the sample information and tracking information the day before shipping specimens.

Include a copy of the Specimen Requisition Form (Appendix B) with your shipment.

CaTissue will store a complete record of the biopsy samples that are collected and analyzed as part of this study.

Please email the DFCI study coordinator [redacted] and DFCI Core Lab [redacted] with the sample information and tracking information the day before shipping biopsy specimens.

5.9 Research Blood Sample Collection

Research blood collection is mandatory for all patients for DNA isolation and cell-free circulating DNA analysis. Collection tubes for research blood samples will be provided in the research biopsy/blood collection kit available from Core Prognostex. The samples will be banked in the DF/HCC Core and Blood Tissue Bank to extract germline and cell-free DNA to be used as normal DNA reference for tumor tissue-based studies and for future research purposes. These specimens will become the property of the DF/HCC.

The following research blood samples are required:

- Two 10 mL lavender top (EDTA Fisher #366643) tubes of whole blood at baseline (or at any time after registration but before surgery).
- Two 10 mL Streck tubes will be collected at baseline, after registration but before treatment initiation, and at the pre-surgery visit (4 total). The baseline tubes will be collected after registration, but before treatment begins on Day 1.
- Three 10 mL CPT tubes will be collected at baseline and at the pre-surgery visit. The baseline sample should be collected any time after registration but before treatment initiation.

All samples should be de-identified and labeled with the Participant initials, Participant Study ID number and date of collection and time point (e.g., "Baseline" or "Off Treatment"). Processing instructions are provided in the table below.

Include a copy of the Specimen Requisition Form (Appendix B) with your shipment.

It is recommended that the baseline specimens be collected on the same day as the research biopsy so the research blood can be shipped in the biopsy-shipping container provided by the study. All blood samples should be shipped overnight Monday – Thursday at ambient temperature to:

Ashka Patel
Brigham and Women's Hospital
Breast Tissue/Blood Bank
Thorn Building - Room 428
20 Shattuck Street
Boston, MA 02115

If Friday collection cannot be avoided:

- Purple top (EDTA) tubes should be processed for whole blood and serum, aliquoted into cryovials, stored and -80C and shipped on dry ice to the above address on the next possible business day
- Streck tubes should be kept at ambient temperature and shipped ambient to above address on the next possible business day. DO NOT FREEZE STRECK TUBES
- CPT tubes should be kept refrigerated and shipped on a cold pack to above address on the next possible business day.

Sample Type	Processing Instructions
Lavender Top Tubes: Whole Blood for genomic analysis	Collect 20 cc of whole blood by standard venous phlebotomy into the EDTA (purple top) tubes provided. Tube should be labeled with patient study number, patient initials, and date / time of collection. After collection, invert the tubes 10 times to ensure adequate mixing and anticoagulation. DO NOT centrifuge this tube. Store tube at room temperature until ready for shipment. Ship in the ambient temperature (cold pack) compartment of the shipping kit. Do not freeze.
Streck Tubes: Circulating cfDNA	Collect 20 mL of whole blood into 2 x 10 ml Streck BCT tubes Invert tubes 10 times Streck tubes should be kept at 6°C (42.8°F) to an ambient temperature of 37°C (98°F) until shipping. Do not freeze.
CPT Tubes (blue and black tiger top tubes): PBMCs	Collect 10 mL of whole blood into three 10 ml CPT tubes Centrifuge sample at 1600 rpm for 30 minutes at room temperature CPT tubes should be kept at 4°C until shipment lying sideways (horizontally) Ship sample on cold pack ASAP, no later than 24 hours after collection Do not freeze.

Please email the DFCI study coordinator [redacted] the DFCI Core Lab [redacted]

[redacted] with the sample information and tracking information the day before shipping specimens.

5.10 Agent Administration

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.10.1 Window Phase

The first part or window phase of the study will include 120 postmenopausal women diagnosed with either invasive lobular carcinoma (n=60 participants) or invasive ductal carcinoma (n= 60 participants). The treatment is described below in Table 2. In the window phase, patients will be randomized to receive either tamoxifen (Arm A) or letrozole (Arm B) for a total duration of two weeks. Tamoxifen and Letrozole are commercial agents and will be billed to the patient's insurance.

Patients should receive a minimum of 14 days of letrozole or tamoxifen and treatment should not be interrupted until the research biopsy is performed (i.e. patients should be on treatment at the time of research biopsy).

Patients randomized to receive letrozole in the window phase may receive continuous letrozole dosing without break between the window and treatment phase.

Table 2: Treatment regimen – Window Phase

Agent	Pre-medications	Dose	Route	Schedule	Cycle Length
Arm A					
Tamoxifen	No routine premedication required	20mg	PO	Once Daily on days 1-14 (continuous)	14 days
Arm B					
Letrozole	No routine premedication required	2.5mg	PO	Once Daily on days 1-14 (continuous)	14 days

5.10.2 Treatment Phase

The second part of the study – Treatment Phase – will include up to 195 participants, compromised of 120 patients first treated in the window phase, and the rest of the patients enrolled directly into the treatment phase of the study. Premenopausal patients will be enrolled directly into the treatment phase of the study. The treatment is described below

in Table 3. In the treatment phase of the study patients will be randomized to receive Arm C: endocrine therapy plus Palbociclib or Arm D: endocrine therapy alone. Postmenopausal patients will receive letrozole. Premenopausal patients will receive tamoxifen and ovarian suppression with LHRH agonist

One cycle is defined as 4 weeks (28 ± 3 days). Patients will be treated for a total of six cycles. Study treatment will be administered in 28-day/4-week cycles if no additional time is required for reversal of toxicity. If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend that preclude performance of the procedure within the allotted 3-day window, the procedure should be performed on the nearest following date.

Endocrine therapy may continue after the completion of 24 weeks until surgery at the discretion of the treating investigator.

Patients randomized to Arm C will be offered up to six cycles of palbociclib with endocrine therapy as postoperative (adjuvant) therapy (inclusive of neoadjuvant therapy, the total duration is equivalent to 1 year).. Patients randomized to endocrine therapy alone (Arm D) will be offered postoperative (adjuvant) treatment with palbociclib given in combination with endocrine therapy for 12 cycles (a total duration of 1 year). See section 5.14 for more information about prescribing adjuvant palbociclib.

Table 3: Treatment regimen – Treatment Phase

Agent	Pre-medications; precautions	Dose	Route	Schedule	Cycle Length
Arm C					
Palbociclib	Given with or without food	125 mg	PO	Once Daily on days 1-21, followed by one week off	28 days (4 weeks)
For Postmenopausal Patients					
Letrozole	No routine premedication required	2.5mg	PO	Once Daily on days 1-28 (continuous)	
For Premenopausal Patients					
Tamoxifen	No routine premedication required	20mg	PO	Once Daily on days 1-28 (continuous)	
Arm D					
For Postmenopausal Patients					
Letrozole	No routine	2.5mg	PO	Once Daily on days	28 days

	premedication required			1-28 (continuous)	(4 weeks)
For Premenopausal Patients					
Tamoxifen	No routine premedication required	20mg	PO	Once Daily on days 1-28 (continuous)	
Mandated for Premenopausal Patients on Arm C and D					
LHRH agonist	No routine premedication	Dose recommended by the manufacturer	IM	Recommended once monthly depot injection	28 days (4 weeks)

5.10.3 Endocrine Therapy – Non Investigational Product(s)

Endocrine therapy (letrozole or tamoxifen) should be taken orally, once per day, as per standard dosing. Patients should be instructed to record daily administration of the study drugs in a drug diary (Appendix C for the Window portion, Appendix D for the Treatment portion). Ordering of endocrine therapy self-administration relative to palbociclib self-administration is as per patient preference. LHRH agonists will be administered to premenopausal woman in the treatment phase according to standard institutional or regional practice. Generics are allowed, if locally available.

Specific storage conditions, handling dispensation and administration instructions have to be locally followed according to local regulations and in accordance with respective local package inserts and/ or local SmPCs. Expected toxicities and potential risks can be obtained from respective local pack inserts and or local SmPCs. Missed doses of endocrine therapy should not be made up.

If palbociclib is held or delayed for toxicity, endocrine therapy should continue as planned.

Endocrine therapy may continue after the completion of 24 weeks until surgery at the discretion of the treating investigator.

A study team member should review the drug diary for the endocrine therapy but does not need to perform a pill count for letrozole or tamoxifen.

5.10.4 Palbociclib

Palbociclib 125 mg should be taken orally, once per day, with or without food. If a dose is vomited, a replacement dose should NOT be taken. If a dose is missed, and it is less than 6 hours from usual time of dosing, then patients may take that dose. Otherwise that

dose should be skipped and NOT retaken; patients should resume regular dosing the following day. Patients who inadvertently take 1 extra dose during a day must skip the next day's dose. Patients should be instructed to record daily administration of the study drugs in a drug diary (Appendix D). Treatment is continuous daily for 21 days, and then 7 days off, to complete a 28 day cycle. Participants must meet lab eligibility criteria for Cycle 1 Day 1. Subsequent cycles must meet retreatment criteria outlined in Section 6.3.2.

On days when patient is scheduled for a clinic visit, the patient may take the oral medications at home or in the clinic. In addition, patients will bring blister packs to visits, and pill counts will be performed as follows: Patients will be required to return all blister packs of palbociclib as well as the completed drug diary at each study visit for drug accountability. Drug accountability for palbociclib will be performed at each study visit prior to dispensing drug supply for the next cycle(s). The number of remaining tablets will be documented and recorded.

A study team member should review the drug diary for the endocrine therapy but does not need to perform a pill count for letrozole or tamoxifen.

5.11 General Concomitant Medication and Supportive Care Guidelines

Permitted Ancillary Medications

Supportive care medications are allowed at any time on trial, as long as they are not included in the list of prohibited medications based on CYP induction (detailed below).

Specifically, the following agents are permitted:

- Antiemetics
- Antidiarrheal therapy
- Antiallergic measures such as corticosteroids and antihistamines
- Bisphosphonates: Patients being treated with bisphosphonates for management of osteoporosis when they enter the study and may continue the medication as long as the dose is stable. Patients may also initiate bisphosphonate therapy while on protocol therapy if medically indicated.
- Agents to assist in management of endocrine therapy-induced side effects (Nonsteroidal anti-inflammatory drugs [NSAIDs], gabapentin, duloxetine, venlafaxine, etc.).
- Diabetes management medication including metformin
- Rank Ligand Inhibitors

Non-breast surgery is allowed during protocol therapy. Patients pursuing this surgery must hold palbociclib therapy approximately 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.

Prohibited Concomitant Medications

Growth factors, including Granulocyte Colony Stimulating Factor (G-CSF), are not allowed on trial (with the exception of situations where a patient becomes clinically and medically unstable due to neutropenia). The use of concurrent investigational or other antitumor therapies, other than endocrine therapy, is not permitted for study patients. If a subject must take one of the following medications during the study, and there is no alternative, the subject needs to discontinue palbociclib.

CYP3A Inhibitors/Inducers

Potent (Strong/Moderate) 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 potent CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans. The concurrent use of the following compounds is not allowed in the study:

- Strong CYP3A inducers, including carbamazepine, phenytoin, primidone, rifampin, rifapentin, and St. John's wort.
- Strong CYP3A inhibitors, including, boceprevir, clarithromycin, conivaptan, delavirdine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit.
- Moderate CYP3A inhibitors including amprenavir, atazanavir, diltiazem, erythromycin, fosamprenavir, verapamil.
- Moderate CYP3A inducers including felbamate, nevirapine, phenobarbital, rifabutin.

Anticancer Therapies

No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, radiation therapy or endocrine therapy other than those allowed in the protocol will be permitted during the study.

Hormone replacement therapy, topical estrogens (but not intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators not indicated in the protocol design, e.g. raloxifene, are prohibited during the window and treatment phase.

Medications Not Recommended

The following treatments are not recommended throughout the duration of the study. Alternative therapies should be considered whenever possible:

The concurrent use of dexamethasone is not recommended.

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.

The use of herbal medicine is not recommended during the study.

CYP3A Substrates with a Narrow Therapeutic Index: The dose of the sensitive CYP3A4 substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced when given concurrently with palbociclib as palbociclib may increase their exposure.

5.12 Definitive Breast Surgery

Definitive breast surgery (excision and/or mastectomy) must be performed no later than 42 days from the completion of six cycles (24 weeks) of treatment in the treatment phase of the study (within 42 days of C6D28). If contralateral mastectomy is performed concurrently, the pathology report from the contralateral breast must be reported if invasive disease is identified.

5.13 Post-operative Radiotherapy

Decisions regarding choice of post-surgical radiotherapy will be made by the treating team.

5.14 Post-operative Adjuvant Therapy

The treating team will make decisions regarding choice of post-surgical adjuvant therapy.

Treating physicians will be permitted to prescribe palbociclib from investigational supply as post-operative adjuvant therapy under the following guidelines:

Arm C: Up to 6 cycles of Palbociclib in combination with endocrine therapy as additional post-surgical therapy for patients randomized to Palbociclib and endocrine therapy (Arm C) in the treatment phase of the study.

- It is recommended that patients on Arm C be monitored for neutropenia via CBC on day 1 of every cycle. Palbociclib may be dispensed up to 3 cycles at a time
- Participants on this arm should start therapy at the dose and frequency they were receiving during the neoadjuvant phase. Dose holds/reductions/interruptions are recommended based on the individual patient's safety and tolerability, as assessed by the treating physician.

Arm D: Up to 12 cycles of Palbociclib in combination with endocrine therapy as additional post-surgical therapy for patients randomized to endocrine therapy alone (Arm D) in the treatment phase of the study.

- It is recommended that patients on Arm D be monitored for neutropenia via CBC on day 1 of every cycle and Day 15 of Cycles 1 and 2. After the completion of 2 cycles, Palbociclib can be dispensed up to 3 cycles at a time.

  - The recommended starting dose is 125 mg by mouth once a day with food for 21 days followed by 7 days off treatment. Dose holds/reductions/interruptions are recommended based on the individual patient's safety and tolerability, as assessed by the treating physician.

- Palbociclib will be provided by [redacted] at no cost.
- There is no protocol-mandated monitoring (labs, assessments, toxicity, or drug compliance). All therapy will be prescribed per investigator discretion. Please refer to the Palbociclib (IBRANCE) package insert for additional guidance.
- Participants on either arm may begin their adjuvant palbociclib at any time and there is no restriction on when therapy can begin after surgery. For example, it would be permissible for a patient to start their adjuvant therapy 6 or 12 months after their surgery.
- Toxicity data related to adjuvant Palbociclib will not be recorded in the eCRFs.

5.15 Criteria for Taking a Participant off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for 6 cycles (24 weeks) or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Otto Metzger, MD. [redacted]

5.16 Duration of Follow Up

The first post-surgery follow-up visit will be considered the subject's final study visit. If breast surgery is not performed the subject's final visit will be the 30 days after the last dose of protocol-specified therapy.

Simplified post-surgery follow-up and treatment information will be subsequently collected. Decisions regarding choice of post-surgical treatment and disease assessments will be at the discretion of the treating team and not mandated by the current protocol. Additional post-surgical palbociclib given in combination with endocrine therapy may be given at the discretion of the treating physician, but this is not mandated by the current protocol. Physicians will be allowed to prescribe up to six cycles of palbociclib in combination with endocrine therapy ONLY for patients randomized to receive endocrine therapy alone. The investigator is not required to actively monitor patients for adverse events after the final visit. However, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that is considered related to the study medication

Post-surgery follow-up information will be collected at assessments every year until 10 years after surgery, or until a disease-free survival event.

Disease-free survival (DFS) will be defined from the time of randomization until the occurrence of the first of the following events:

- Local/regional recurrence: a recurrent or new invasive ipsilateral breast cancer, invasive breast cancer in the axilla, regional lymph nodes, chest wall, or skin of the ipsilateral breast.
- Contralateral invasive breast cancer
- Distant recurrence: metastatic disease that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer. A single new lesion on a bone scan without evidence of lytic disease on x-ray and without symptoms does not in and of itself constitute distant recurrence, but multiple new bone lesions, or increased isotope uptake associated with new bone symptoms are more likely due to metastases. Bone metastases must be documented with x-rays and clinical description.
- Death from any cause

In situ cancer is not included as a DFS event. If a patient has in situ breast cancer (on the ipsilateral or contralateral side) diagnosed during follow-up before any of the DFS events above, then the patient should continue to be followed for DFS on study (even if she is given hormonal therapy after the in situ diagnosis).
If a patient is diagnosed with a non-melanoma skin cancer or a vaginal carcinoma in situ, she will continue on this study and continue to be followed for DFS.

It is recommended that any disease-free survival event should be biopsied to confirm recurrent disease. Information on breast cancer status, new anti-cancer therapy, and new onset malignancy diagnoses will be collected via simplified CRFs. Following an DFS event, survival information (i.e., date and cause of death or last known alive date if not deceased and new onset malignancy information) will be collected. All patients will be followed for survival.

5.17 Criteria for Taking a Participant off Study

Participants will be removed from study before study completion when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Otto Metzger, MD [redacted]

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

A list of the important adverse events and potential risks associated with Palbociclib appear below and will determine whether dose delays and modifications will be made and whether the event requires expedited reporting in addition to routine reporting.

6.1 Endocrine Therapy

The most common adverse events experienced with use of letrozole include hot flashes, arthralgia, and gradual loss of bone density. The most common adverse events experienced with use of tamoxifen include hot flashes, night sweats, and vaginal discharge. Venous thromboembolic disease and endometrial cancer are rare risks of tamoxifen. A detailed description of AEs of the commercially available endocrine therapy agents used in this study should be obtained from the particular package inserts (SmPCs) of the locally obtained commercial supplies.

6.1.1 Expected Toxicities for Letrozole

- Hot flashes
- Hyperhidrosis
- Fatigue
- Headache
- Insomnia
- Hypertension
- Abdominal pain
- Dizziness
- Arthralgia
- Myalgia
- Weakness
- Anorexia
- Nausea
- Edema
- Constipation
- Weight gain

- Dyspnea
- Cough
- Osteopenia
- Hypercholesterolemia
- Depression
- Anxiety
- Diarrhea
- Dermatitis
- Myocardial infarction
- Death due to stroke or heart failure

6.1.2 Expected Toxicities for Tamoxifen

- Night sweating
- Vaginal discharge or dryness
- Irregular menses
- Vulvar itching
- Nausea
- Edema
- Dermatitis
- Hair thinning
- Elevated liver enzymes
- Osteopenia
- Thrombus
- Cataracts
- A raised sensitivity to blood thinners such as Coumadin
- Endometrial changes

6.2 Palbociclib

The primary anticipated toxicity of palbociclib is neutropenia. In the phase I, dose-escalation trial of palbociclib alone in advanced cancers, neutropenia was the only dose-limiting toxicity (DLT). Grade 3 neutropenia during cycle 1 was observed in 3/22 patients receiving palbociclib 125 mg PO daily, with no grade 4 neutropenia events observed. Based on this result, 125 mg PO daily became the recommended phase 2 dose (RP2D). Other hematologic AEs of grade 3 or greater during cycle 1 were anemia and leukopenia, occurring in 1 and 4 of 41 patients, respectively. The most common non-hematologic AEs of grade 3 or greater during cycle 1 were fatigue, nausea, and abdominal pain (each occurring in 2 of 41 patients). Of note, there were no complicated hematologic AEs documented, and all hematologic AEs resolved during the off-drug period of a 3-week on/1 week off schedule, and were non-cumulative.

In a phase II trial of palbociclib alone for advanced breast cancer, the only toxicities $\geq$ grade 3 observed were transient neutropenia (50%) and thrombocytopenia (21%)[56]. In a phase II trial

of palbociclib plus letrozole for first-line therapy of hormone receptor positive breast cancer, the most common AEs reported were neutropenia, leukopenia, and fatigue[57, 58]. The median time to first treatment delay for neutropenia was 58 days, and the median duration of treatment delay until recovery was 5 days (range 1-16 days, [redacted] internal data). In general, hematologic abnormalities were adequately managed with standard supportive care, were not complicated, and resolved during the drug hold with no cumulative toxicity noted.

The Single Reference Safety Document for Palbociclib is the Investigator's Brochure for the compound.

6.2.1 Expected Toxicities for Palbociclib

- Neutropenia
- Decrease neutrophil count (without fever)
- Fatigue
- Anemia
- Diarrhea
- Nausea
- Thrombocytopenia
- Decreased appetite
- Constipation
- Mouth blisters/sores
- Infection of the sinus or lung
- Vomiting
- Loss of touch or sensation of pins and needles or numbness on the skin
- Inflammation of the mouth
- Pain including: Abdominal pain, mouth/throat pain, back pain, flank pain, muscle pain, bone pain, pain in the hands and feet.
- hair loss
- Rash
- Cough
- Shortness of breath
- Headache
- Dizziness
- Hot flush
- Insomnia
- Bloating
- Swelling in extremities
- Nosebleed
- Muscle spasm or cramps
- Fever
- Dry mouth
- Fever with dangerously low white blood cell count

- Abnormal taste
- Abdominal pain
- Indigestion
- Feeling week and having no energy
- Flu-like illness
- Increase in blood liver enzymes
- Dry skin
- Itching in the mouth or throat
- High blood pressure
- Depression
- Increased risk of fall
- Irritation or sores in the lining of hollow organs
- Abdominal swelling
- Chills
- Runny Nose
- Night Sweats
- Decreased sense of touch or sensation
- Weight loss
- Low blood pressure
- Hearts beats that are fast and hard
- Blurred vision
- Increased tearing
- Dry eye
- Abnormal electrical conduction within the heart
- Pulmonary embolism
- Pneumonitis

6.3 Dose Modification Guidelines

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of palbociclib and/or endocrine therapy may need to be adjusted.

Incidence, nature, and severity of adverse events triggering dose or study treatment modifications are to be assessed by the investigator and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0) as AE related dose and treatment modification recommendations are based on this grading scale.

6.3.1 Dose Modifications / Toxicity Management – Endocrine Therapy

No dose reduction for endocrine therapy is permitted. In the window phase of the study, no treatment interruption is allowed. In the treatment phase of the study, endocrine treatment interruption is allowed for up to 4 consecutive weeks for endocrine therapy-related toxicities or

personal reasons as per the investigator's best medical judgment. It is important to note that if a patient encounters difficulty tolerating endocrine therapy, the treating provider should make all possible efforts to continue the patient on neoadjuvant endocrine therapy, including the use of supportive medication (e.g. ibuprofen), while continuing treatment with palbociclib.

Subjects missing more than 4 cumulative weeks of endocrine therapy will be removed from treatment phase of the study and will also stop palbociclib (i.e. for those randomized to receive palbociclib). Patients who discontinue endocrine therapy and/or palbociclib will continue to be followed according to post treatment follow up as defined in Schedule of Assessments.

6.3.2 Dose Modifications / Toxicity management – Palbociclib

Dose or treatment modifications for palbociclib are allowable and may occur as *dose interruptions* (within a cycle), *dose delays* (between cycles) or *dose reductions*.

In the event of significant palbociclib treatment-related toxicity, palbociclib dosing may be interrupted or delayed or reduced as described within this section and according to table below.

In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Dose Reductions Section unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied, the patient may need to return to the clinic to receive new drug supply.

Palbociclib Dosing Interruptions/Delays

In general, cycles should be 28 days long unless the start of a new cycle is delayed.

Doses missed within a cycle (meaning dose interruptions) are not made up. If, e.g. the AE resolves before the end of the cycle, then the patient can resume taking the palbociclib for the remainder of the cycle but should still stop on Day 21 to maintain the 7-day break.

If an adverse event requiring a dose hold has not resolved by Day 1 of the next planned cycle, the start of the new cycle should be delayed according to guidelines within this section,.

Patients on palbociclib arm experiencing one or more of the following adverse events described below should have their palbociclib treatment interrupted/delayed until criteria for retreatment are met:

- Uncomplicated Grade 3 or 4 neutropenia (ANC < 1000/mm3).
- Grade 3 or 4 neutropenia (ANC < 1000/mm3) associated with a documented infection or fever ≥ 38.5°C, 100.4°F.
- Grade 3 or 4 thrombocytopenia (Platelet count < 50,000/mm3)
- Grade ≥ 3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment).
- Grade 2 non-hematologic toxicity persisting despite optimal medical treatment, lasting more than 3 weeks, and unacceptable to patient and/or provider.
- In case of concurrent occurrence of > 3x ULN ALT and 2x ULN Total Bilirubin, at any time during the trial, palbociclib will be permanently discontinued.

Patients should not hold or discontinue palbociclib for side effects potentially or likely related to concomitant standard endocrine therapy (e.g., grade 3 or long lasting grade 2 joint pain) as per the investigator's judgment.

Follow up assessments according to investigator's decision should be performed until adequate recovery occurs as assessed by the Investigator.

Subjects missing more than 4 cumulative weeks of endocrine therapy will be removed from treatment phase of the study and will also stop palbociclib (i.e. for those randomized to receive palbociclib). For a patient who chooses to stop palbociclib, it is strongly recommended to encourage the patient to continue neoadjuvant endocrine therapy for a total duration of six cycles.

Palbociclib Retreatment Criteria

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

- Platelet count ≥ 75,000/mm^3;
- ANC ≥ 1000/mm^3 and no fever;
- Any persistent grade 2, grade 3 or higher treatment-related non-hematologic AEs considered related to palbociclib have recovered to Grade ≤ 1 or baseline.

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

If the retreatment parameters are met within 4 weeks of treatment interruption or cycle delay, palbociclib may be resumed.

If these parameters have not been met after 4 weeks of dose interruption (including the scheduled

1 week off treatment) or cycle delay, the patient should permanently discontinue palbociclib treatment.

Palbociclib Dose Reductions

- The palbociclib dose may need to be reduced, following a dose interruption or cycle delay when treatment is resumed.
- No specific dose adjustments are recommended for Grade 1 or short lasting Grade 2 (< 4 weeks) treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances and document the changes in the CRF.
- For palbociclib related, Grade 2 toxicity lasting for ≥ 4 weeks (excluding alopecia) or for palbociclib related Grade 3 toxicities (despite maximum supportive care as judged by the investigator), palbociclib dose reduction is recommended for all subsequent cycles. Taking palbociclib according to recommendation (i.e., with food) should be reinforced and confirmed. Dose reduction of palbociclib by one dose level, and, if needed, by two dose levels as described in the table below may be required depending on type and severity of the toxicity encountered. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation of palbociclib from 100mg to 125 mg is not allowed. Cautious dose re-escalation from 75mg to 100mg can be considered per investigator discretion. Patients requiring more than 2 dose reductions will discontinue palbociclib treatment.

Table 4: Palbociclib Dose Levels and Dose Reduction Schedule

Dose Level	**Palbociclib once daily on days 1-21, followed by 7 days off**
Starting dose	125 mg/d
Level -1 (first dose reduction)	100 mg/d
Level -2 (second dose reduction)	75 mg/d
Discontinue palbociclib treatment	

Palbociclib recommended dose modifications for treatment-related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 5.

Table 5: AE triggered Dose Modifications and Treatment Management for Palbociclib		
CTCAE v.4.0 Adverse Event	**CTCAE v.4.0 Grade**	**Intervention with Palbociclib**

Neutropenic fever *(ANC <1000/mm³ associated with fever ≥38.5 °)*	3, 4	*Hold until clinically stable, if ANC recovers (ANC ≥ 1000mm³) and absence of fever,* then *1st appearance:* resume at next lower dose *2nd appearance:* resume at next lower dose *≥3rd appearance:* Discontinue
Neutrophil count decreased *(ANC <1000/mm³)* *Note: The use of growth factors is not allowed*	3	*Hold until ≥ 1000/mm3,* then *1st appearance*: resume at same dose level *2nd appearance:* resume at next lower dose *3rd appearance:* resume at next lower dose
	4	*Hold until ≥ 1000/mm*3, then *1st appearance*: resume at next lower dose *2nd appearance:* resume at next lower dose *≥3rd appearance:* Discontinue
Platelet count decreased (platelet count < 50,000)	3	*Hold until ≥ 75000/mm*3, then *1st appearance:* Maintain dose *2nd appearance:* resume at next lower dose *3rd appearance:* resume at next lower dose
	4	*Hold until ≥ 75000/mm*3, then *1st appearance:* resume at next lower dose *2nd appearance:* resume at next lower dose *≥3rd appearance:* Discontinue
Anemia (Hgb <8.0 g/dL)	3, 4	*Reduce to next lower dose only in cases of protracted symptomatic anemia considered to be related to palbociclib*

Alanine aminotransferase (ALT) increased with total bilirubin < 2X ULN (in the absence of cholestasis or hemolysis)	3	*Hold until clinically stable and recovered to ≤ Grade 1 or to baseline,* then *1st appearance:* resume at same dose *2nd appearance:* resume at next lower dose *≥3rd appearance:* Discontinue (If grade 3 ALT or AST elevation does not recur after at least 4 weeks following re-treatment with palbociclib, the dose may be escalated by single dose level)
	4	*Hold until clinically stable and recover to ≤ Grade 1 or has returned to baseline,* then *1st appearance:* resume at next lower dose *2nd appearance:* discontinue
Concurrent > 3 X ULN ALT (SGPT) and 2 X ULN total bilirubin		Discontinue immediately
Interstatial Lung Disease or Pneumonitits	2	Hold until clinically stable and recovered to baseline
	3, 4	Permanently discontinue palbociclib
Other AEs requiring dose modification per investigator *(Note: Investigator must determine attribution of AE and only follow dose modifications for the causal agent.)*	2	*Lasting Less than 4 weeks*: Maintain Dose *Lasting 4 weeks (excluding alopecia) or more despite maximal supporting care unacceptable to patient and/or investigator, and thought to be related to palbociclib*: resume at next lower dose
	3, 4	If the AE is related to palbociclib, withhold until symptoms resolve to: • ≤ Grade 1 or to baseline • ≤ Grade 2 (if not considered a safety risk for the patient) Resume at the next lower dose level.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial.

7.1 Monitoring of Adverse Events and Period of Observation

The study period, during which AEs and SAEs must be reported, begins after starting the first dose of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to study treatment.
All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be assessed and reported, when appropriate. Abnormal laboratory values will not be reported unless deemed to be clinically significant based on the criteria listed in section 7.7. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to Palbociclib or Endocrine Therapy, expectedness, and actions taken. The following list of expected toxicities (Section 7.2) and the characteristics of an observed AE (Section 7.3) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.2 Expected Toxicities

7.2.1 Expected toxicities for Endocrine Therapy

The most common adverse events experienced with use of letrozole include hot flashes, arthralgia, and gradual loss of bone density. The most common adverse events experienced with use of tamoxifen include hot flashes, night sweats, and vaginal discharge. Venous thromboembolic disease and endometrial cancer are rare risks of tamoxifen. A list of expected toxicities it available in protocol section 6.1 or from the particular package inserts (SmPCs) of the locally obtained commercial supplies for a more detailed description.

7.2.2 Expected toxicities for Palbociclib

The primary anticipated toxicity of palbociclib is neutropenia. In the phase I, dose-escalation trial of palbociclib alone in advanced cancers, neutropenia was the only dose-limiting toxicity (DLT). Grade 3 neutropenia during cycle 1 was observed in 3/22 patients receiving palbociclib 125 mg PO daily, with no grade 4 neutropenic events observed. Based on this result, 125 mg PO daily became the recommended phase 2 dose (RP2D). Other hematologic AEs of grade 3 or greater during cycle 1 were anemia and leukopenia, occurring in 1 and 4 of 41 patients, respectively. The most common non-hematologic AEs of grade 3 or greater during cycle 1 were fatigue, nausea, and abdominal pain (each occurring in 2 of 41 patients). Of note, there were no complicated hematologic AEs documented, and all hematologic AEs resolved during the off drug period of a 3 week on/1 week off schedule, and were non-cumulative.

A list of expected toxicities it available in protocol section 6.2.

In a phase II trial of palbociclib alone for advanced breast cancer, the only toxicities > grade 3 observed were transient neutropenia (50%) and thrombocytopenia (21%). In a phase II trial of palbociclib plus letrozole for first-line therapy of hormone receptor positive breast cancer, the most common AEs reported were neutropenia, leukopenia, and fatigue. The median time to first treatment delay for neutropenia was 58 days, and the median duration of treatment delay until recovery was 5 days (range 1-16 days). [redacted] internal data). In general, hematologic abnormalities were adequately managed with standard supportive care, were not complicated, and resolved during the drug hold with no cumulative toxicity noted.

In the phase I, dose-escalation trial of palbociclib alone in advanced cancers, QT interval changes were also evaluated in detail. While 26 of 41 patients had a maximum increase of <30 msec from baseline QTc, zero patients had an on-treatment value exceeding 500 msec.

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

- **Expectedness:**
  Expected adverse events are those adverse events that are listed or characterized in the current adverse event list, the Package Insert, the Investigator Brochure or is included in the informed consent document as a potential risk.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.4.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.4.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy. Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events in addition to the DF/HCC reporting requirements below.

Additionally, the overall PI should be notified of SAEs that meet the DF/HCC definition of a reportable AE within the timeframes detailed in the table below using the institutional SAE form.

The Coordinating Center will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

Table 6: DF/HCC Reportable Adverse Events

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					

* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.

7.5 Expedited Reporting to [redacted]

Within 24 business hours of first awareness of the event (immediately if the event is fatal or life threatening), the study team from the site where the SAE took place will report to [redacted] by facsimile or email 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 study subjects or individuals otherwise exposed to [redacted] Product as described below. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

Investigators will report SAEs using Form FDA 3500A (MedWatch). *The Reportable Event Fax Cover Sheet* provided by [redacted] must also be included with each SAE submitted. The *Reportable Event Fax Cover Sheet* can be found in Appendix F.

7.5.1 SAE Definition for Reporting to [redacted]

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.

7.5.2 Exposure During Pregnancy, Exposure During Lactation, Occupational Exposure

Even though there may not be an associated SAE, exposure to Palbociclib during pregnancy, exposure to Palbociclib during lactation, and occupational exposure to the Palbociclib are reportable t[redacted]

7.5.3 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 [redacted] If a participant 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.

7.5.4 SAE Reporting Period

The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Palbociclib through 30 calendar days after the last administration of the Palbociclib, or longer if so specified in the Protocol. In addition, if a Principal Investigator becomes aware of an SAE occurring any time after the administration of the last dose of the Palbociclib, the Principal Investigator should report that SAE to [redacted] the Principal Investigator suspects a causal relationship between the Palbociclib and the SAE.

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

All grade 2 or higher adverse events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. Abnormal laboratory values or diagnostic tests will not be reported on the case report forms unless they induce clinical signs or symptoms, require treatment or further diagnostic tests, or result in a dose hold or modification. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Sections 6 and 7.2.

Refer to the Investigator's Brochure for detailed Palbociclib information and FDA approved package inserts for more information about commercial agents.

8.1 Tamoxifen

8.1.1 Description

Tamoxifen tablets for oral administration contain 30.4 mg of tamoxifen citrate which is equivalent to 20 mg of tamoxifen, a nonsteroidal antiestrogen. Tamoxifen is the trans-isomer of ariphenylethylene derivative. The chemical name is (Z)2-[4-(1,2-diphenyl-1-butenyl) phenoxy] N, N-dimethylethanamine 2-hydroxy-1,2,3- propanetricarboxylate (1:1). Tamoxifen citrate has a molecular weight of 563.62, the pKa' is 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/mL and in 0.02 N HCl at 37°C, it is 0.2

mg/mL.

8.1.2 Form

Tamoxifen is available in 20 mg tablets.

8.1.3 Storage and Stability

Store at controlled room temperature, 20-25°C (68-77°F) [see USP Controlled Room Temperature].

8.1.4 Compatibility

No compatibility issues exist for co-administration of palbociclib and tamoxifen.

8.1.5 Availability

Tamoxifen is commercially available.

8.1.6 Administration

The recommended dose of tamoxifen is 20 mg once daily.

8.2 Letrozole

8.2.1 Description

A letrozole tablet for oral administration contains 2.5 mg of letrozole, a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis). It is chemically described as 4,4'-(1H-1,2,4-Triazol-1ylmethylene) dibenzonitrile, and its structural formula is Letrozole is a white to yellowish crystalline powder, practically odorless, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. It has a molecular weight of 285.31, empirical formula C17H11N5, and a melting range of 184°C-185°C.

8.2.2 Form

Letrozole is available in 2.5 mg tablets.

8.2.3 Storage and Stability

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

8.2.4 Compatibility

No compatibility issues exist for co-administration of palbociclib and letrozole.

8.2.5 Availability

Letrozole is commercially available.

8.2.6 Administration

The recommended dose of letrozole is one 2.5 mg tablet administered once a day, without regard to meals.

8.3 Palbociclib

8.3.1 Description

Chemical name: 6-acetyl-8-cyclopentyl-5-methyl-2-(5-(piperazin-1-yl)pyridin-2-ylamino) pyrido[2,3-d]pyrimidin-7(8H)-one.
Chemical formula: C24H29N7O2
Molecular weight: 447.54.
Half life: ~29 hours.
Plasma protein binding of palbociclib: ~85%
Plasma protein binding of PF-05089326 (the lactam of palbociclib, one of the main metabolites present in plasma): 95%

Palbociclib (IC_{50} = 11 nM; Ki = 2 nM) 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 and SULT2A1 enzymes. Information on potential drug interactions can be found in section 5.4.

8.3.2 Form

Palbociclib will be supplied by [redacted] as smooth-coated tablets containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. [redacted] will supply the oral drug formulation to sites in monthly cartons of blister packs containing 75 mg, 100 mg, or 125 mg tablets. Each carton will contain three blister packs each containing a one-week supply of tablets. The tablets can be differentiated by their size, color, and carton color.

8.3.3 Storage and Stability

Storage conditions stated in the Single Reference Safety Document (i.e. Investigator's Brochure (IB), United States Package Insert (USPI), Summary of Product Characteristics (SPC), or Local Product Document (LPD)) will be superseded by the label storage.

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

Investigators and site staff are reminded to check temperatures daily (i.e. manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for room storage. Any temperature excursions must be reported to [redacted] The investigational products must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to [redacted]

Once a deviation is identified, the investigational products (palbociclib) must be quarantined and not used until [redacted] provides documentation of permission to use the investigational product.

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

8.3.4 Compatibility

No compatibility issues exist for co-administration of palbociclib.

8.3.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.3.6 Availability

Palbociclib will be supplied free-of-charge from [redacted] commercial supply of drug.

8.3.7 Administration

Palbociclib will be provided in non-patient-specific cartons of blister packs containing either 75 mg, 100 mg or 125 mg capsules.

Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty blister packs should be returned to the site at the next study

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 blister packs provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, tablets must not be crushed and/or mixed into any vehicle for oral ingestion; tablets must be swallowed intact.

Only a single tablet 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 tablets will be dispensed.

8.3.8 Ordering

Qualified personnel at participating sites will order the drug directly from [redacted]

8.3.9 Accountability

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

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Biomarker Analysis

Tumor samples obtained from diagnostic FFPE sides, core biopsies, surgical specimen sampling, and liquid biopsies will be used to assess the potential prognostic or predictive value of candidate markers or biomarker panels, improve diagnostic tests, improve understanding of breast cancer biology, or discover new biomarker profiles related to treatment benefit and/or safety or disease characteristics. Refer to section 5.8 and 5.9 for tissue and blood collection, handling and shipment instructions.

Correlative samples will be analyzed by Dana-Farber Cancer Institute with collaboration from the participating institutions and the Broad Institute at MIT.

9.1 Biomarker linked to study primary objective

9.1.1 Central Pathology Assessments

Central pathology assessment will be performed at the Brigham and Women's Pathology core.

Central IHC staining for Ki67, estrogen (ER) and progesterone receptor (PgR) will be performed following consensus recommendations [59, 60]. Ki67 staining will be performed in three time points: diagnostic tissue, research biopsy tissue and residual tumor. Hormone receptors will be assessed at baseline and in residual tumors.
E-cadherin/p120 staining will be performed on all samples as previously reported [61]. E-cadherin is scored as positive or negative membrane staining and P120 scored as positive membrane (i.e. observed in IDC) or cytoplasmic (ILC). E-cadherin/p120 staining will be performed using baseline diagnostic tissue or research biopsy specimen.

9.2 Biomarkers linked to correlative studies

9.2.1 Solid biopsies

DNA extracted from core biopsies will be profiled by a hybrid capture-based targeted massively parallel sequencing test able to screen for coding sequencing mutations, indels, copy number alterations, and selected rearrangements from > 300 genes of interest.

The essential features of the screening assay are summarized as follows:

- Be able to test for all point mutations, indels, copy number changes, and selected rearrangements in all the genes of interest
- Be able to be run on 10-20 FFPE slides
- Have demonstrated high sensitivity and specificity, especially in samples with relatively low tumor purity (e.g., having high *minimum* depth of coverage across all regions of interest)

Comprehensive sequencing approaches such as whole exome sequencing or whole genome sequencing may be performed in lieu of a targeted approach. A final decision on the best sequencing modality will be made before the planned analysis.

Of importance, somatic mutations identified while profiling tumor samples could also be present in the patient's DNA and could be passed to subsequent generations. To the present date, there is no consensus on the type of findings on a tumor-sequencing assay that would imply the presence-absence of mutation. Sequencing of germline DNA may be needed to allow the appropriate interpretation of somatic events.

Tumor and/or germline findings will be communicated to the treating clinician with advice to consider germline testing if clinical and/or family history is consistent with the presence of such abnormality.

RNA extracted from core biopsies will be profiled using RNA-Seq technology

In addition, we will use determine the SET 2,3 Index using the MD Anderson platform on research biopsy samples and the FFPE slides. This will be used to evaluate samples for factors that may predict patients who are better candidates for neoadjuvant endocrine-based treatment. This analysis will be performed at MD Anderson.

9.2.2 Prioritization of molecular assays

DNA- and RNA-based assays will be performed after adequate tumor tissue is secured for the co-primary endpoints of the study. RNA-based assays will be performed using frozen tumor biopsies.

9.2.3 Liquid biopsies

Cell-free Circulating DNA may be a source of tumor DNA where genetic analysis can be done. The current protocol will investigate whether molecular alterations found in tumor biopsies are detectable in peripheral circulation. The field of "liquid biopsies" is evolving quickly and we expect to use the most updated sequencing approach to study the collected samples. We expect to use a multi-gene targeted sequencing approach or whole exome sequencing for the analysis of cell free tumor DNA. Profiling will be performed at the Broad Institute of MIT with analysis at Dana-Farber Cancer Institute.

10. STUDY CALENDAR

All subjects must sign an informed consent document prior to initiation of any study related procedures.

Baseline evaluations (laboratory tests and other non-laboratory tests) must be performed within 28 days of study entry with the exception of the following tests: Documentation of MRI, mammogram, or ultrasound (including DCIS and invasive cancer) of the diseased breast performed within 42 days prior to registration. Mammogram for the unaffected contralateral breast is required within 12 months prior to registration. Serum or urine pregnancy test must be negative in women judged premenopausal within 7 days of randomization, or in women with amenorrhea of less than 12 months at time of randomization.

All assessments must be performed prior to administration of any study medication. Day 15 study assessments should be performed within $\pm$ 3 days of the protocol-specified date, unless otherwise noted. There is a $\pm$ 3 day window for day 1 of Cycles 1-6 on the treatment phase.

Screening Phase (for window phase and treatment phase): All screening evaluations must be completed and reviewed to confirm that patients meet all inclusion criteria and do not meet any of the exclusion criteria before randomization. **If screening assessments occur within 7 days before Window or Treatment Day 1, then they may serve as the Window or Treatment Day 1 assessments also and do not need to be repeated.** Participants randomized to receive Palbociclib must meet lab eligibility criteria for Treatment Day 1. Subsequent cycles with Palbociclib must

meet retreatment criteria outlined in Section 6.3.2.

Window Phase: It is strongly recommended to schedule the 2-week image-guide research biopsy prior to treatment initiation. Image-guided research biopsy must be performed within +/- 3 days after the 2-week window period. A minimum of 14 days of letrozole or tamoxifen is recommended. Treatment should not be interrupted until the research biopsy is performed (i.e. patients should be on treatment at the time of research biopsy).

Treatment phase: should start within 7 days + 2 days after the window phase research core biopsy. There is a +/- 3-day window for day 1 of Cycles 1-6 on the treatment phase. Patients assigned to Arm C (receiving palbociclib) will have safety laboratory testing performed at C1D15 and C2D15. This laboratory testing can be performed at a local laboratory or at the research center, but results need to be available and reviewed by the research team before treatment can continue.

Follow-up: Post-surgery follow-up information will be collected at assessments annually until 10 years after surgery. No tests or procedures are required during follow-up but clinical data will be collected on CRFs. These data should be based on exams, tests, or procedures done at the registering institution or at a local facility. Data to be collected from all patients include adjuvant cytotoxic (+/- targeted) treatment, adjuvant endocrine (+/- targeted) treatment, date and site of all recurrences, date and cause of deaths as well as date and diagnosis of secondary malignancies.

Table 8. Schedule of assessment for patients enrolled in the window phase of the study

Parameter	Screening	Window Phase (14 days)		Treatment Phase (Cycle 28 days)			Pre-Surgery [a]	Post Surgery[b]
				Cycle 1 and 2		Cycles 3 to 6		
Day	-28 to 0	Window D1	Window D15	D1	D15	D1	within 42 days of last cycle	Within 42 days after surgery
Time Window			+/-3	+/- 3 days	+/-3	+/-3 days	-2days	
Informed consent	X							
Complete medical history	X							
Physical exam/ Vital signs	X	X		X		X	X	
Performance status (ECOG)	X	X						
Adverse Event evaluation	X	X		X		X	X	X
Concomitant meds	X							
Hematology [c]	X			X [h]	X [h, i]	X [h]	X [h]	
Chemistry [d]	X			X [h]		X [h]	X [h]	
Pregnancy test [e]	X							
Breast Imaging [f]	X						X	
Axillary evaluation [g]	X							
Tissue collection (Section 5.8)	X	X	X[j]					X
Research blood		X					X	

collection (Section 5.9)								
Candidate for breast conservation evaluation	X						X	

a) Pre-surgical imaging must occur within 42 days of completion of treatment (with a -2 day window).
b) Follow-up information will be collected yearly until 10 years after surgery. No tests or procedures are required during follow-up but clinical data will be collected on CRFs. These data should be based on exams, tests, or procedures done at the registering institution or at a local facility. Data to be collected from all patients include adjuvant cytotoxic (+/- targeted) treatment, adjuvant endocrine (+/- targeted) treatment, date and site of all recurrences, date and cause of deaths as well as date and diagnosis of secondary malignancies.
c) Hematology includes hemoglobin, white blood cell count (WBC), absolute neutrophils, and platelet count.
d) Chemistry includes AST (SGOT)/ALT (SGPT), alkaline phosphatase, sodium, potassium, total calcium, total bilirubin, serum creatinine, total protein and albumin.
e) Serum or urine pregnancy test for women of childbearing potential (≤ 7 days prior randomization).
f) Baseline imaging within 42 days prior to enrollment; MRI is strongly recommended, although other imaging modalities (mammogram, ultrasound) are permitted if practical or financial considerations preclude MRI, as long as the target lesion can be adequately measured. This same imaging modality should be performed again prior to surgery. Mammogram of the unaffected contralateral breast is required within 12 months prior to registration.
g) For women with clinically suspicious lymph nodes, preoperative axillary ultrasound with fine needle aspiration or core biopsy of suspicious should be performed. For subjects with a clinically negative axilla, a sentinel lymph node biopsy should be performed either before or after preoperative therapy at the discretion of the subject's physicians. Axillary evaluation must be done within 42 days prior to enrollment.
h) Hematology and chemistry are not required for Arm D patients at the specified time points.
i) Arm C patients only. Testing can be performed at a local laboratory or at the research center.
j) It is strongly recommended to schedule the image-guide research biopsy at window phase D15 prior to window phase treatment initiation. See Section 5.8 for details.

Table 9. Schedule of assessment for patients enrolled directly into the treatment phase of the study

Parameter	Screening	Treatment Phase			Pre-Surgery [a]	Post surgery [b]
		Cycle 1 and 2		Cycles 3 to 6		
Day	-28 to 0	D1	D15	D1	Within 42 days of last cycle	Within 42 days after surgery
Time Window		+/- 3 days	+/-3 days	+/- 3 days	-2 days	
Informed consent	X					
Complete medical history	X					
Inclusion/Exclusion	X					
Physical exam/Vital signs	X	X		X	X	
Performance status (ECOG)	X					
Adverse Event evaluation	X	X		X	X	X
Concomitant meds	X					
Hematology [c]	X	X [h]	X [h, i]	X [h]	X [h]	
Chemistry [d]	X	X [h]		X [h]	X [h]	
Pregnancy test [e]	X					
Breast Imaging [f]	X				X	
Axillary evaluation [g]	X					

Tissue Collection (Section 5.8)	X	X C1D15 only	X[j] C1D15 only			X
Research Blood collection (Section 5.9)		X			X	
Candidate for breast conservation evaluation	X				X	

a) Pre-surgical imaging must occur within 42 days of completion of treatment (with a -2 day window).
b) Follow-up information will be collected yearly until 10 years after surgery. No tests or procedures are required during follow-up but clinical data will be collected on CRFs. These data should be based on exams, tests, or procedures done at the registering institution or at a local facility. Data to be collected from all patients include adjuvant cytotoxic (+/- targeted) treatment, adjuvant endocrine (+/- targeted) treatment, date and site of all recurrences, date and cause of deaths as well as date and diagnosis of secondary malignancies.
c) Hematology includes hemoglobin, white blood cell count (WBC), absolute neutrophils, and platelet count.
d) Blood chemistry includes AST (SGOT)/ALT (SGPT), alkaline phosphatase, sodium, potassium, total calcium, total bilirubin, serum creatinine, total protein and albumin.
e) Serum or urine pregnancy test for women of childbearing potential (≤ 7 days prior randomization).
f) Baseline imaging within 42 days prior to enrollment; MRI is strongly recommended, although other imaging modalities (mammogram, ultrasound) are permitted if practical or financial considerations preclude MRI, as long as the target lesion can be adequately measured. This same imaging modality should be performed again prior to surgery. Mammogram of the unaffected contralateral breast is required within 12 months prior to registration
g) For women with clinically suspicious lymph nodes, preoperative axillary ultrasound with fine needle aspiration or core biopsy of suspicious should be performed. For subjects with a clinically negative axilla, a sentinel lymph node biopsy should be performed either before or after preoperative therapy at the discretion of the subject's physicians. Axillary evaluation must be done within 42 days prior to enrollment.
h) Hematology and Blood chemistry are not recommended for Arm D at the specified time points.
i) Arm C patients only. Testing can be performed at a local laboratory or at the research center
j) It is strongly recommended to schedule the image-guide research biopsy at C1D15 prior to treatment initiation. See Section 5.8 for details.

Table 10. Required Research Specimen Submissions

Specimen Type	**Time Point**							**Shipping Condition**
	Screening	**Window Phase [a]**		**Treatment Phase [b]**		**Pre-Surgery**	**Post Surgery**	
		D1	**D15**	**C1D1**	**C1D15**			
Block or Unstained FFPE slides	X						X	Ambient
20 mL whole blood in lavender top (EDTA) tube		X		X				Ambient
Two 10 mL Streck tubes of whole blood		X		X		X		Ambient
Three 10 mL CPT tube for PBMCs				X		X		Ambient
Core biopsies in formalin		X	X	X	X			Ambient

Core biopsies in OCT		X	X	X	X			Frozen, Dry ice

a. Only for pts who enroll in the window phase first (Arm A and B patients)
b. Only for pts who enroll in treatment phase directly.

Refer to protocol section 5.8 for details about tissue and biopsy collection, processing, and shipping details. Refer to protocol section 5.9 for blood sample collection, processing, and shipping details.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

A baseline and presurgical radiographic study of the breast is required; MRI is recommended. The same radiographic modality should be used consistently. The baseline scan must be obtained within 42 days prior to enrollment. The presurgical scan should occur 2-6 weeks (Day 14-42) after the last cycle ends. If the participant clinically progresses, repeat imaging is required. If there is discordance (clinical progression, but radiographic stable disease or response), contact the study chair.

11.2 Radiographic assessment

Each participant will have pre- and post-therapy radiographic tumor measurements, preferably by MRI, however if logistic or practical issues preclude MRI use, mammogram or ultrasound may be substituted. In the event of multifocal or multicentric disease in the breast, the investigator must determine which will represent the target lesion(s). This should remain consistent throughout the study. The target lesion(s) should be selected on the basis of its size and suitability for accurate repetitive measurements following RECIST 1.1 recommendations.

Response criteria are based on the RECIST 1.1 criteria:

Radiographic Complete Response (CR): Complete disappearance of the target lesion

Radiographic Partial Response (PR): Greater than or equal to 30% decrease in the longest diameter (LD) of the target lesion taking as reference the baseline LD

Radiographic Progressive Disease (PD): Greater than or equal to 20% increase in the LD of target lesion taking as reference the baseline LD or the appearance of one or more new lesions

Radiographic Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the baseline LD

11.3 Clinical assessments

Both target and, in the event of multifocal or multicentric invasive cancer, nontarget lesions

should be followed clinically. If the participant demonstrates clinical progression at any time, repeat imaging is required. If there is discordance (clinical progression, but radiographic stable disease or response), study PI should be contacted to solve discordance.

11.4 Pathologic Response

Pathologic response will be reported using the Residual Cancer Burden calculator [62] M.D Anderson http://www.mdanderson.org/breastcancer_RCB.

The following parameters are required from pathologic examination in order to calculate Residual Cancer Burden (RCB) after neoadjuvant treatment:

- The largest two dimensions (mms) of the residual tumor bed in the breast (largest tumor bed if multicentric disease)
- Histologic assessment of the percentage of the tumor bed area that contains carcinoma (all carcinoma, i.e. invasive and in situ), select one of the following: 0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%
- To assess cellularity it is helpful to scan across the sections of tumor bed and then estimate the average cellularity from the different microscopic fields.
- When estimating percentage cancer cellularity in any microscopic field, compare the involved area with obvious standards, e.g. more or less than half, one quarter, one fifth, one tenth, one twentieth, etc.
- Expect there to be variable cellularity within the cross section of any tumor bed, but estimate the overall cellularity from the average of the estimates in different microscopic fields of the tumor bed. E.g., if cellularity in different fields of the tumor bed were estimated as 20%, 10%, 20%, 0%, 20%, 30%, then an average estimate of overall cellularity would be 20%.
- Histologic estimate of the percentage of the carcinoma in the tumor bed that is in situ, select one of the following: 0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%
- The number of positive (metastatic) lymph nodes
- The largest diameter (mm) of the largest nodal metastasis

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The ODQ/CTRIO will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the ODQ/CTRIO according to the schedule set by the ODQ/CTRIO .

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix E.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12.4 Collaborative Research and Future Use of Data and Biospecimens

Tissue, blood, bodily fluids, and other materials derived from these will be collected in this study to analyze genes, DNA, RNA, proteins and cells for the study's correlative endpoints and potential future research, utilizing new types of biomarker testing as it becomes available.

These samples and any data generated as a part of these clinical trials may be used for future research studies and may be provided to collaborating investigators both within and outside of the DF/HCC for either correlative endpoints or secondary use. Samples and data may be shared with outside non-profit academic investigators, as well as with for-profit pharmaceutical investigators

or commercial entities, with whom we collaborate. When samples or data are sent to collaborators and when any research is performed on them, all information will be identified with a code, and will not contain any PHI, such as name, birthday, or MRNs.

In order to allow the greatest amount of research to be performed on the specimens and information generated as a part of this trial, researchers in this study may share results of genetic sequencing with other scientists. De-identified specimen or genetic data may be placed into one of more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). The results from the correlative research on this study will be shared with these public databases. Through such databases, researchers from anywhere will have access to de-identified samples or data for future research. More detailed information, beyond the public database, may only be accessed by scientists at other research centers who have received special permission to review de-identified data.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open label phase II neoadjuvant clinical trial of Palbociclib in combination with endocrine therapy for ER+ early-stage breast cancer. The planned sample size is up to 195 participants. The study includes a "window of treatment" phase followed by a treatment phase. Patients will be randomized to treatment assignment to each phase upon enrollment.

In the window phase, patients will be randomized in a 1:1 ratio to receive a two-week course of tamoxifen or letrozole. A research biopsy will be obtained before and after completion of two-week course of endocrine therapy. In the treatment phase participants will be randomized in a 2:1 ratio to receive endocrine therapy in combination with palbociclib or endocrine therapy monotherapy for a total duration of 24 weeks. Patients will be randomized with strata defined by histology, initial lymph node status (positive vs. negative) and pre-treatment tumor size (T1-2 vs. T3).

Study enrollment will be performed as follows: Postmenopausal women diagnosed with either invasive lobular carcinoma (n= 60) or invasive ductal carcinoma (n=60) will be eligible to enroll in the window phase of the study as specified above and would continue on study into the treatment phase. Premenopausal patients will be eligible to enroll directly into the treatment phase of the study. Upon completion of enrollment of either the invasive lobular carcinoma or invasive ductal carcinoma subsets in the window phase, the study will be amended such that subsequent postmenopausal patients will be eligible to enroll directly into the treatment phase of the study. A total of 75 patients will be enrolled directly into the treatment phase of the study.

The study has two co-primary objectives. In the window phase, the primary objective is to evaluate the difference in anti-proliferative activity of letrozole versus tamoxifen within cohorts of ER+ breast cancer for patients with invasive lobular and invasive ductal carcinoma. The endpoint for anti-proliferative activity will be fold-change in percent Ki67 staining from baseline to day 15. In the treatment phase of the study the primary objective is to compare the pathologic

response of endocrine therapy + palbociclib versus endocrine therapy alone in breast cancer patients diagnosed with hormone receptor positive invasive breast cancer, as determined by the Residual Cancer Burden (RCB). Secondary clinical endpoints include clinical response, safety and tolerability defined under CTCAE version 4.0

13.2 Sample Size, Accrual Rate and Study Duration

The sample size of the study was selected to have adequate power in the window phase to differentiate the difference in anti-proliferative activity of letrozole versus tamoxifen in subgroups of patients with invasive lobular and ductal carcinoma. Sample size was expanded in the treatment phase in order to compare pathologic response in all patients treated with letrozole with palboccilib versus letrozole monotherapy.

With 60 patients per histologic subtype randomized 1:1 to tamoxifen or letrozole, and assuming 10% of paired samples will not be evaluable for Ki67, n=27 patients per group will provide >90% power for each comparison to detect a difference of 1 standardized unit when using a two-sided Wilcoxon-rank sum test with alpha = 0.05. In evaluating short–term changes of Ki67 during neoadjuvant treatment of primary breast cancer, Dowsett et al. (2005) reported a -59.5% change with tamoxifen (95% CI -68.5 to -47.9). Using these results to estimate the standard deviation (~5.4%) in measured changes in Ki67 in the general population, this target difference in this study would correspond to an increase in anti-proliferative activity to a –65.2% change with letrozole.

No restriction for histological subtype (i.e. invasive lobular or invasive ductal) is imposed for the treatment phase patients. The endpoint for pathologic response will be determined by the RCB index, measured on a continuous scale, at the time of surgery. With 65 patients on treatment with endocrine therapy and 130 patients on treatment with endocrine therapy plus palbociclib, there will be an 80% power for detecting a difference of 0.44 standardized units using a two-sided Wilcoxon-rank sum test with alpha = 0.05. This assumes

- Standard deviation of RCB index is 1 in both treatment groups (based on results in Symmans et al (2007)
- Median RCB index in patients on endocrine therapy is 3.36, which under an assumption of normality corresponds to 2.3% patients having RCB index≤1.36 that corresponds to pathologic complete response.
- Median RCB index in patients on endocrine therapy + palbociclib is 2.92, which under an assumption of normality corresponds to 5.9% patients having RCB index≤1.36 that corresponds to pathologic complete response.

It is expected that it would take approximately 42 months to complete accrual. An additional 6 months of follow-up will be required on the last participant accrued to cover the time from initial enrollment to the post-operative, off-study visit.

13.3 Interim Monitoring Plan

No interim analysis will be conducted for the primary endpoints of the window and treatment phases of this study. The DF/HCC DSMB will monitor toxicity.

13.4 Analysis of Primary Endpoints

Window Phase

Descriptive statistics will be used to summarize the percentage of Ki67 staining measured at baseline and at day 15. The evaluation of change in Ki67 will be performed on the log-scale. For the primary objective, we will evaluate the effects of endocrine therapy within each histology subtype. A Wilcoxon-rank sum test with two-sided alpha = 0.05 will be used to compare the changes in Ki67 in patients treated with letrozole versus tamoxifen and test the null hypothesis of no difference.

Treatment Phase

For the primary objective, we will evaluate the effect of including palbociclib with endocrine therapy compared to endocrine therapy alone on pathologic response among all patients. The difference RCB index between patients receiving endocrine therapy and patients receiving endocrine therapy plus palbociclib will be compared using a Wilcoxon-rank sum test with two-sided alpha = 0.05.

13.5 Analysis of Secondary Endpoints

Window Phase

In secondary analyses we will estimate the relative effect of letrozole vs tamoxifen in patients with ductal histology subtype compared to lobular subtype. The hypothesis is that the improvement in anti-proliferative activity and achievement of cell-cycle arrest is stronger in patients with lobular histology compared to ductal histology. This will be assessed using a logistic regression model with outcome being achieving cell cycle arrest at end of window phase. Cell cycle arrest is defined to be percentage of Ki67<2.7. The model will include main effects for treatment and histology and an interaction between treatment and histology, adjusting for baseline Ki67. If the interaction term is statistically significant, we will conclude that the effect of letrozole vs tamoxifen is different in patients with ductal and lobular histologies.

Treatment Phase

In secondary analyses, we will use linear models (or nonlinear models if necessary) to understand the effect of treatment on RCB index, adjusting for tumor size, nodal status and menopausal status at baseline. An additional secondary analysis will consider the binary outcome of RCB 0/II (continuous RCB index≤1.36) to measure pathologic complete response. We will compare the treatment arms using a Fisher's exact test. We will also use a Cochran-Mantel-Haenszel test to evaluate treatment effect stratified by endocrine backbone (or equivalently, menopausal status) and additional factors such histology, lymph node status and tumor size if the number of responses within subgroups allows for asymptotic assumptions to be reasonable. In addition, we will include patients who were excluded from the primary analysis of RCB index because they do not have an RCB score due to receiving chemotherapy prior to surgery. These patients will be treated as having no pathologic complete response.

The central modified Preoperative Endocrine Therapy Prognostic Index (mPEPI) will be defined as 0 (good prognosis), 1–3 (intermediate) and 4+ (poor prognosis). We will describe the distribution of the categorical PEPI score in patients receiving endocrine therapy alone versus endocrine therapy + palbociclib. We will use exact tests to compare the distribution of PEPI scores in each treatment group.

We will estimate the clinical response rate, defined as the number of partial and complete responses, after preoperative endocrine therapy + palbociclib and endocrine therapy alone and associated 95% Wilson score confidence intervals.

Participants will be evaluated for toxicity from the time of their first treatment, and rates of adverse events and treatment modification or discontinuation will be reported with 95% Wilson score confidence intervals.

Among all patients that entered the trial during the treatment phase, we will have a research biopsy at baseline (pre-treatment), two weeks after starting treatment and then specimen collection at surgery. We will first compare change in Ki67 at surgery compared to baseline, stratified by the endocrine backbone (or equivalently, menopausal status) in all patients. We will then focus on the pre-menopausal women recruited into the treatment phase and first compare the change in Ki67 from baseline to two weeks.

The association of correlative biomarkers to histological subtypes and clinical outcomes in the treatment phase will be exploratory and hypothesis generating, and will not adjust for multiple comparisons in any statistical inferences.

Secondary objectives will use two-sided alpha = 0.05 for all inferential tests

13.6 Correlative Science Objectives

For the 75 patients who enroll directly on the treatment phase of the study, a pre-treatment and 2-week is required to assess the correlation of Rb phosphorylation and % change in Ki67. The analysis plan to assess the correlation of changes from baseline will be as follows: if Gaussian assumptions are shown to hold under Box-Cox transformation of Ki67 and Rb, we will report the Pearson product moment correlation coefficient and 95% confidence interval, and use the Fisher Z transformation to test whether the correlation is greater than a null value of 0.8. If Gaussian assumptions fail to hold, we will report the Spearmen correlation coefficient with an empirical 95% confidence interval drawn from the BCA bootstrap method to assess whether the null value is excluded. Assuming that 80% of patients provide pairs of specimen evaluable for each biomarker, 60 patients will provide 82.6% power to reject the null if the true rho = 0.91.

13.7 Exploratory Axillary Lymph Node Surgery Objectives

The lymph node surgery objectives will utilize information already necessary and collected for the primary and secondary endpoint analyses (for example RCB, mPEPI, and clinical response rates). Nodal response will be compared between treatment arms. Overall nodal response will be measured in terms of 1) clinical nodal downstaging (i.e. cN1 to cN0, or cN2 to

cN1/0) and 2) histologic nodal response. We will measure the following histologic features of the lymph nodes within each treatment arm to determine histologic nodal response: 1) largest size of lymph node metastasis (isolated tumor cells, micrometastases, or macrometastases); 2) presence (yes/no) and type of stromal fibrosis (dense vs loose); 3) percent tumor cellularity of the lymph node metastasis; and 4) presence of extranodal extension. We will study the association between in-breast Ki67 staining response to neoadjuvant endocrine therapy (one-time Ki67 levels obtained on the 2-week research biopsy as well as the delta from baseline to 2-week biopsy, already collected for the secondary endpoint analysis) and nodal response after 24 weeks of neoadjuvant endocrine therapy. We will estimate summary statistics and graphically examine, via boxplots, the biomarker levels at 2 weeks and change in biomarker levels for patients that did and did not have a nodal response, for each treatment group.

We will determine the rates of various axillary surgeries (no axillary surgery, sentinel lymph node biopsy alone, sentinel lymph node biopsy followed by axillary lymph node dissection, and upfront axillary lymph node dissection) among cN0 and cN1 patient populations. We will use two-way contingency tables to characterize the nodal status pre- and post-endocrine therapy for each treatment arm (the percentage of patients that are cN0 pre-endocrine therapy but pN+ post-endocrine therapy and that are cN+ pre-endocrine therapy and have persistent pN+ disease post-endocrine therapy), stratified by histologic subtype (ductal/lobular). Among the sentinel lymph node biopsy alone and sentinel lymph node biopsy followed by axillary lymph node dissection groups, we will describe the number of positive nodes and size of largest nodal metastasis (isolated tumor cells, micrometastases 0.2mm - 2mm, and macrometastasis > 2mm).

A critical variable in the characterization of axillary surgical management after preoperative therapy is the surgeon's decision making. We will conduct a mixed-methods study of the axillary surgeries in PELOPS via semi-structured interviews among the surgeons who treated patients on this trial to explore their rationale for choice of axillary surgery following neoadjuvant endocrine therapy. Phone consent for semi-structured interviews will be obtained without a waiting period, prior to beginning the interview. The planned interview guide is based on the comprehensive, integrated checklist of determinants of practice[68]. In partnership with DFCI's Survey and Data Management Core, the interview guide (APPENDIX G) will be refined through iterative review and pilot tested for validity. Interviews will be conducted until saturation of theme is reached, they will be transcribed verbatim, and then coded using a grounded theory approach[69]. Power is not applicable because sample sizes are fixed. It is estimated that 20-24 surgeons will be surveyed in total, from a mix of academic, private, and community practices.

Lastly, we will estimate 3-year axillary recurrence rates in the PELOPS trial based on axillary surgery (sentinel lymph node biopsy or axillary lymph node dissection), compared by treatment arm and controlling for clinical characteristics including but not limited to adjuvant radiation therapy received, age, histology (ductal, lobular, mixed), histologic grade, multicentric disease, lymphovascular invasion, clinical T category, clinical N category, breast surgery performed. We are expecting recurrence rates of less than 2% at 3 years, based on the recurrence rates observed in prior axillary treatment trials among patients undergoing upfront surgery[70,71].

13.8 Reporting and Exclusions

13.8.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment. Participants who never start protocol therapy will be considered unevaluable.

13.8.2 Evaluation of the Primary Efficacy Endpoint

All patients who receive at least one dose of study drug in the treatment phase will be evaluable for efficacy endpoints. Participants who never start protocol therapy as part of the treatment phase will be considered invaluable. The primary analysis of the window and treatment phase will be conducted under intention-to-treat principles with groups defined by randomized treatment assignment. Biomarker analyses will be conducted in all patients with evaluable biospecimen within arm that is defined by the treatment received (per protocol).

14. PUBLICATION PLAN

The results should be made public within approximately 6 months of the end of data collection. The results of the window phase of the study may be presented prior to the completion of the treatment phase of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B SPECIMEN REQUISITION FORM

Complete this form and include with the specimen shipment. Label ALL materials with participant initials, DFCI participant study ID, and the date the specimen was obtained. Include a pathology report with any archival tissue specimens being submitted.

Ship Fresh Specimen(s) to:

[redacted]

Specimen Information

Participant Initials (FML): _____ Participant Study ID Number: _____ DFCI Assigned MRN: _____

Date specimen(s) shipped: _____

Time Point: ☐ Screening ☐ Window Day 1 ☐ Window Day 15 ☐ Treatment Day 1 ☐ Treatment Day 15 ☐ Pre-surgery ☐ Surgery

Site of tumor: ☐ Right breast ☐ Left breast Pathology reports included (Mark all that apply) ☐ Pre-treatment ☐ Post-treatment

Specimen Type *(indicate inclusion in shipment by checking box)*	**Pathology Number(s) or Serial Coding**	**Quantity submitted**	**Date specimen obtained**	**Time from resection to fixative immersion**
☐ Two 10 ml Whole Blood Lavender (EDTA) Top Tubes				
☐ Two 10 ml Whole Blood Streck Tubes				
☐ Two 10 ml CPT Tubes				
Core biopsy				
☐ Core biopsies in formalin				Minutes
☐ Core biopsies frozen				Minutes
☐ Surgical block ☐ Slides				
☐ Other, specify:				

Responsible contact:_____ **Email:** _____

APPENDIX C STUDY PARTICIPANT DRUG DIARY- WINDOW

PATIENT INSTRUCTIONS:

Take your medications exactly as prescribed by your doctor. See the next page for specific doses for each medication that you are taking on this study.

Continue taking your medication until the date of your biopsy procedure. If you take more than 14 days of medication, record the additional days on the extra lines on the diary on the next page. These are shaded in gray. These lines are only to be completed if you take more than 14 days of medication leading up to your biopsy.

STUDY PARTICIPANT SELF-ADMINISTERED DIARY: ENDOCRINE THERAPY

Participant Name: _____ Cycle #: _____

STUDY DRUG INSTRUCTIONS: Take one _____ on Days 1 – 14. Record the dose of each medication on the chart to the right after taking each day.

	Date	Time	Number of Pills Taken	Comments
Ex:	6/1/2009	8 : 15 ☒ AM ☐ PM	1	Vomited 1 hour later
Day 1		: ☐ AM ☐ PM		
Day 2		: ☐ AM ☐ PM		
Day 3		: ☐ AM ☐ PM		
Day 4		: ☐ AM ☐ PM		
Day 5		: ☐ AM ☐ PM		
Day 6		: ☐ AM ☐ PM		
Day 7		: ☐ AM ☐ PM		
Day 8		: ☐ AM ☐ PM		
Day 9		: ☐ AM ☐ PM		
Day 10		: ☐ AM ☐ PM		
Day 11		: ☐ AM ☐ PM		
Day 12		: ☐ AM ☐ PM		
Day 13		: ☐ AM ☐ PM		
Day 14		: ☐ AM ☐ PM		
Day 15		: ☐ AM ☐ PM		
Day 16		: ☐ AM ☐ PM		
Day 17		: ☐ AM ☐ PM		

Patient Signature: _____ Date: _____/___/_____

APPENDIX D STUDY PARTICIPANT ADMINISTERED DRUG DIARY- TREATMENT

PATIENT INSTRUCTIONS:
Take your medications exactly as prescribed by your doctor. See the next page for specific doses for each medication that you are taking on this study.

- Keep Palbociclib capsules in the bottle(s) provided and do not transfer them to any other container. Store at room temperature.

Palbociclib should be taken by mouth once per day at approximately the same time each day together with food. There is no timeframe specified in which participants should eat when taking palbociclib.

- During Cycles 1 and 2 you will have blood work done on Day 15. Please do not take the next day's drug (Day 16) until a provider calls you to discuss the results.
- Capsules must be swallowed whole. Do not soak capsules or empty contents into any food or drink.
- If you vomit after taking Palbociclib, do NOT take another dose. Please note any vomiting in the **Comments** section of the diary on the next page.
- If a dose is missed and it is less than 6 hours from usual time of dosing, then you may take that dose. Otherwise that dose should be skipped and NOT taken. You should resume regular dosing the following day. If you miss a dose, record "0" for Number Taken on the next page.
- If you accidentally take an extra dose during a day skip the next day's dose and record the extra dose on the next page.

The use of the following compounds is not allowed in the study:

- Strong CYP3A inducers, including carbamazepine, phenytoin, primidone, rifampin, rifapentin, and St. John's wort.
- Strong CYP3A inhibitors, including, boceprevir, clarithromycin, conivaptan, delavirdine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit.
- Moderate CYP3A inhibitors including amprenavir, atazanavir, diltiazem, erythromycin, fosamprenavir, verapamil.
- Moderate CYP3A inducers including felbamate, nevirapine, phenobarbital, rifabutin.

<table>
<tr><th colspan="3">FOR CLINIC USE ONLY:</th></tr>
<tr><td rowspan="4">Give patient all 4 pages of Drug Diary stapled together. Provide one diary per cycle (28 days).
Complete patient identifiers and medical team contact information on pages 2-5.
Complete date of last Palbociclib dose n page 2 and the name of endocrine therapy on page 4.
When patient returns pill bottles and diary perform a Palbociclib pill count and record adherence information in the box to the right OR in the patient record.</td><td colspan="2">Staff Initials:</td></tr>
<tr><td>Date Dispensed:</td><td>Date Returned:</td></tr>
<tr><td># Palbociclib capsules dispensed:</td><td># Palbociclib capsules returned:</td></tr>
<tr><td colspan="2"># Palbociclib capsules that should have been taken:</td></tr>
<tr><td colspan="3">Discrepancy Notes:</td></tr>
</table>

STUDY PARTICIPANT SELF-ADMINISTERED DIARY: PALBOCICLIB (Cycles 1-2)

Participant Name: _____ Cycle #: _____

Your Doctor _____ Phone _____

Your Nurse _____ Phone _____

STUDY DRUG INSTRUCTIONS: Take one Palbociclib capsule on Days 1 – 21. Record the dose of each medication on the chart to the right after taking each day.

	Date	Time	Number of Palbociclib Capsules Taken	Comments
Ex:	6/1/2009	8 : 15 ☒ AM ☐ PM	1	Vomited 1 hour later
Day 1		: ☐ AM ☐ PM		
Day 2		: ☐ AM ☐ PM		
Day 3		: ☐ AM ☐ PM		
Day 4		: ☐ AM ☐ PM		
Day 5		: ☐ AM ☐ PM		
Day 6		: ☐ AM ☐ PM		
Day 7		: ☐ AM ☐ PM		
Day 8		: ☐ AM ☐ PM		
Day 9		: ☐ AM ☐ PM		
Day 10		: ☐ AM ☐ PM		
Day 11		: ☐ AM ☐ PM		
Day 12		: ☐ AM ☐ PM		
Day 13		: ☐ AM ☐ PM		
Day 14		: ☐ AM ☐ PM		
Day 15		: ☐ AM ☐ PM		
During Cycles 1 and 2: *Remember to have your lab work done on Day 15. Make sure you speak with your provider before taking the capsule on Day 16.*				
Day 16		: ☐ AM ☐ PM		
Day 17		: ☐ AM ☐ PM		
Day 18		: ☐ AM ☐ PM		
Day 19		: ☐ AM ☐ PM		
Day 20		: ☐ AM ☐ PM		
Day 21		: ☐ AM ☐ PM		

Do not take any Palbociclib after: _____/_____/_____

Patient Signature: _____ Date: _____/_____/_____

STUDY PARTICIPANT SELF-ADMINISTERED DIARY: PALBOCICLIB (Cycle 3-6)

Participant Name: _____ Cycle #: _____

Your Doctor _____ Phone _____

Your Nurse _____ Phone _____

STUDY DRUG INSTRUCTIONS: Take one Palbociclib capsule on Days 1 – 21. Record the dose of each medication on the chart to the right after taking each day.

	Date	Time	Number of Palbociclib Capsules Taken	Comments
Ex:	6/1/2009	8 : 15 ☒ AM ☐ PM	1	Vomited 1 hour later
Day 1		: ☐ AM ☐ PM		
Day 2		: ☐ AM ☐ PM		
Day 3		: ☐ AM ☐ PM		
Day 4		: ☐ AM ☐ PM		
Day 5		: ☐ AM ☐ PM		
Day 6		: ☐ AM ☐ PM		
Day 7		: ☐ AM ☐ PM		
Day 8		: ☐ AM ☐ PM		
Day 9		: ☐ AM ☐ PM		
Day 10		: ☐ AM ☐ PM		
Day 11		: ☐ AM ☐ PM		
Day 12		: ☐ AM ☐ PM		
Day 13		: ☐ AM ☐ PM		
Day 14		: ☐ AM ☐ PM		
Day 15		: ☐ AM ☐ PM		
Day 16		: ☐ AM ☐ PM		
Day 17		: ☐ AM ☐ PM		
Day 18		: ☐ AM ☐ PM		
Day 19		: ☐ AM ☐ PM		
Day 20		: ☐ AM ☐ PM		
Day 21		: ☐ AM ☐ PM		

<u>Do not take any Palbociclib after:</u> _____/_____/_____

Patient Signature: _____ Date: _____/_____/_____

STUDY PARTICIPANT SELF-ADMINISTERED DIARY: ENDOCRINE THERAPY

Participant Name: _____ Cycle #: _____

STUDY DRUG INSTRUCTIONS: Take one _____ on Days 1 – 28. Record the dose of each medication on the chart to the right after taking each day.

	Date	Time	Number of Pills Taken	Comments
Ex:	6/1/2009	8 : 15 ☒ AM ☐ PM	1	Vomited 1 hour later
Day 1		: ☐ AM ☐ PM		
Day 2		: ☐ AM ☐ PM		
Day 3		: ☐ AM ☐ PM		
Day 4		: ☐ AM ☐ PM		
Day 5		: ☐ AM ☐ PM		
Day 6		: ☐ AM ☐ PM		
Day 7		: ☐ AM ☐ PM		
Day 8		: ☐ AM ☐ PM		
Day 9		: ☐ AM ☐ PM		
Day 10		: ☐ AM ☐ PM		
Day 11		: ☐ AM ☐ PM		
Day 12		: ☐ AM ☐ PM		
Day 13		: ☐ AM ☐ PM		
Day 14		: ☐ AM ☐ PM		
Day 15		: ☐ AM ☐ PM		
Day 16		: ☐ AM ☐ PM		
Day 17		: ☐ AM ☐ PM		
Day 18		: ☐ AM ☐ PM		
Day 19		: ☐ AM ☐ PM		
Day 20		: ☐ AM ☐ PM		
Day 21		: ☐ AM ☐ PM		
Day 22		: ☐ AM ☐ PM		
Day 23		: ☐ AM ☐ PM		
Day 24		: ☐ AM ☐ PM		
Day 25		: ☐ AM ☐ PM		
Day 26		: ☐ AM ☐ PM		
Day 27		: ☐ AM ☐ PM		
Day 28		: ☐ AM ☐ PM		

Patient Signature: _____ Date: _____/___/_____

APPENDIX E DF/HCC MULTI-CENTER DSMP

DFCI IRB Protocol #: 16-052

APPENDIX E

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

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SCHEMA 2

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1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures..

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (Food and Drug Administration (FDA), etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol

document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Office of Data Quality (ODQ), formerly Quality Assurance Office for Clinical Trials (QACT): A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Otto Metzger, MD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC ODQ/QACT.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.

- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC

Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be

collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

Please refer to protocol Section 4 for participant registration and treatment assignment information. Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, ODQ requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.9 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.9.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported

by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.10.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.11 Data Management

The DF/HCC ODQ develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC ODQ provides a web based training for eCRF users.

3.11.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ and distributed on a monthly basis.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.

Participating Institutions should order their own agent regardless of the supplier.

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

At a minimum, the Coordinating Center will monitor each participating site twice a year while participants are receiving treatment with a combination of on-site and virtual monitoring. Should a Participating Institution be monitored once and then not accrue any additional patients, then future monitoring visits may not be necessary. The first on site monitoring visit will be triggered by protocol enrollment of three patients.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Additionally, regular and ongoing communication with Participating Institutions will be accomplished by holding all site bi-weekly teleconferences. The Coordinating Center will keep in close touch with the Participating Institutions via email and phone.

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participant's complete medical record and source documents for source documentation verification (SDV) during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled. On site monitoring visits can be supplemented with virtual monitoring assessments, provided that the minimum monitoring frequencies are adhered to.

Virtual Monitoring: The Coordinating Center will request source documentation from Participating Institutions as needed to complete monitoring activities. Participating Institutions will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor. All queries from monitoring visits must be resolved within 30 days of the report being sent.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. Sites are expected to accrue at least 3 patients per year.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the ODQ, assuming at least three participants have been treated on protocol at the site. If significant issues with non-compliance or violations are found that impact participant safety or the integrity of the study are noted at participating sites, the DF/HCC Sponsor will trigger audit of additional participant records.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX F REPORTABLE EVENT COVER SHEET

[redacted]	**REPORTABLE EVENT FAX COVER SHEET (US)**	**01-AUG-2014**

Use this fax cover sheet to fax a reportable event for investigator-initiated research studies

Include with this form the completed [redacted] investigator-initiated research (IIR) serious adverse event (SAE) form, MedWatch Form FDA 3500A-Mandatory Reporting, which can be obtained from the FDA website: www.fda.gov/medwatch/getforms.htm, or other [redacted] agreed-upon form for SAE reporting. If you are using the MedWatch Form to report, the following information should be included in block 5 of the adverse events section:

- The complete clinical course of the patient receiving [redacted] drug
- The causality assessment for each reportable event
- The action taken for each study drug and for each reportable event
- The outcome for each reportable event

This cover sheet MUST be provided with each completed SAE form.

Do not substitute forms/reports or submit additional documentation (such as source documentation) other than what is required.

Do not fax these forms to any additional fax numbers other than the one listed below.

TO: [redacted]	
FAX: [redacted]	
FROM:	DATE:
TELEPHONE:	FAX:
NUMBER OF PAGES (INCLUDING COVER SHEET):	
PRODUCT palbociclib	

PFIZER REFERENCE NUMBER	[redacted]	EXTERNAL REFERENCE NUMBER
STUDY TITLE	Neoadjuvant endocrine therapy with palbociclib for ER-positive invasive lobular and invasive ductal carcinoma	
PATIENT NUMBER		
INVESTIGATOR	Otto Metzger, MD	

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APPENDIX G AXILLARY MANAGEMENT AFTER NEOADJUVANT ENDOCRINE THERAPY FOR HORMONE-POSITIVE BREAST CANCER (SURGEON INTERVIEW GUIDE)

Introduction

Hi, my name is "NAME" and I'm calling from the Dana Farber/Brigham and Women's Cancer Center. Thank you for taking the time to speak with me today. We are speaking with surgeons to better understand their perspectives on axillary surgery after neoadjuvant endocrine therapy. Our discussion today will help inform a survey that will explore issues and attitudes towards the possible omission of axillary lymph node dissection in women with hormone-positive breast cancer treated with neoadjuvant endocrine therapy. It may also inform the design of a future clinical trial testing the omission of axillary lymph node dissection in this population. There are no right or wrong answers in our discussion today, as we are here to better understand your experience and perspectives on the topic at hand.
This interview will be recorded and takes, on average, twenty minutes. Recordings will not be shared with your colleagues, patients or families, or with anyone else outside the research team. I want to be sure that you understand that being part of this interview is voluntary, you can opt to not answer questions or end the conversation at any time. We appreciate your participation in this study. *Obtain informed consent*

Do you have any questions before we begin the interview? *Begin recording*

I. Demographic Information

First off, could I get some baseline information about you?

1) How many years have you been in practice?
2) How would you describe your practice with regards to being academic or community-based or a hybrid model?
3) In what field/specialty, if any, are you board certified?
4) What fellowship training do you have, if any?
5) What is the scope of your surgical practice?
    a) What percentage of your practice is breast surgery?
    b) How many new breast cancer patients do you see per month?
    c) Approximately how many women do you see a month who have hormone-positive breast cancer and are treated with neoadjuvant endocrine therapy?
    d) How do you usually clinically evaluate the axilla in these women (i.e. physical exam and/or U/S?) -*If surgeon routinely uses U/S, ask how they define being "clinically node-negative"*
    e) How do you usually surgically stage the axilla in these women (i.e. ALND or SLNB)?
    -*If surgeon usually performs ALND, ask for further explanation*

For the next set of questions, I am asking you to focus specifically on the management of patients with clinically node-negative, hormone-positive breast cancer, treated with neoadjuvant endocrine therapy.

II. CURRENT PRACTICE

A) Guideline factors

6) Do you know of any pre-existing guidelines for the surgical management of the axilla in this

patient population?

-If yes, how do they influence your practice?

-If no, do you think that guidelines for axillary management in this patient population would be useful?

7) Are you aware of any data evaluating axillary management after neoadjuvant endocrine therapy?

B) Individual Health Professional Factors: Professional Behavior

8) How do you usually approach the decision to evaluate the axillary in this patient population?

-What clinical and disease factors play a role in your decision to evaluate the axillary?

-With this patient population, how often, if ever, do you consider the omission of the axillary evaluation? In what percentage of patients do you actually omit it?

-How has your approach changed over time?

9) If a clinically node-negative patient is found to have positive pathologic nodal disease, how do you approach the decision to perform an axillary lymph node dissection?

-What clinical and disease factors play a role in your decision to evaluate the axillary?

-With this patient population, how often, if ever, do you consider the omission of the axillary lymph node dissection? In what percentage of patients do you actually omit it?

-How has your approach changed over time?

C) Individual Health Professional Factors: Knowledge/Cognitions

If surgeon does omit axillary node dissection:

10) What do you see as the pros and the cons of omitting axillary node dissections?

-For example, what potential consequences might keep you from omitting axillary evaluation?

11) What are your discussions with patients like around axillary dissection/omission?

-For example, to what extent do you counsel patients about whether or not to pursue axillary evaluation?

12) Can you describe any situations in which your patient has preferred to proceed with the axillary dissection even though you offer to omit it?

-How often does this happen?

If surgeon never omits axillary dissection:

13) Overall, how do you feel about the potential omission of axillary dissection in this population?

14) Have you come across any data/studies that explore omission of axillary dissection in this population? If so, what do you think of these data?

D) Patient Factors:

15) From your perspective, what do patients think about omitting ALND? Is it an overall positive or negative for the patient?

16) What impact do you think this practice has on patient outcomes? [probe on reasons behind the impact]

Possible probe: -Do you turn to any particular published data that guide your opinions?

17) What patient factors, if any, would influence your decision to perform ALND?

-Does the patient's breast surgery (i.e. lumpectomy or mastectomy) influence your decision?

E) Professional Interactions

18) Do you think that your surgery colleagues omit ALND? -Do your surgery colleagues influence your decision to omit/perform ALND?
19) Do you routinely discuss these patients at a multi-disciplinary tumor board?
20) Are you influenced in your axillary surgery recommendations by other specialists (i.e. medical oncology or radiation oncology)? -If you omit ALND, do you feel the patient should receive radiation?

F) Social, Political, and Legal Factors

21) Are there any external factors (like financial pressure or incentive, or regulations) that influence your approach to axillary surgery? *Possible probes:*-Do financial incentives or disincentives play a role?
-Or institutional pressures or regulations?
-What about malpractice environment?

III. IN THEORY

A) Individual Health Professional Factors: Cognitions

22) Can you describe any factors or reasons that might keep you from omitting axillary dissection in this population?
Possible probes: -What do you think of the quality of evidence supporting this practice? *[probe on concerns, if any]*
-Do you feel that upfront surgery trial results can be considered in this population? *[probe on concerns, if any]*

B) Professional Interactions: Communication and Influence

23) How would you describe the communication you have, if any, regarding axillary management in this population of patients with your medical oncology or radiation oncology colleagues? *[probe on specifics as needed]*
24) From your experience, how do your medical or radiation oncology view omission of axillary dissection in this population? *[probe on how this is similar or different from surgical view]*
25) Who is usually part of the decision-making process around axillary management?
-For example, do you think your medical or radiation oncology colleagues would like to weigh in on this decision?
26) How, if at all, would decisions around adjuvant treatment change with the omission of axillary dissection? *[radiation, systemic therapy]*

C) Incentives and Resources: Monitoring and Feedback Mechanisms

27) Do you track outcomes among your group or practice?
-In what format do you do so?
-Are the outcomes shared publicly?
28) Do you have a relationship with patient advocates or a patient advocate group at your institution?
-If yes, how do you incorporate their feedback into your practice?
29) Would you feel comfortable recruiting to a clinical trial that plans to omit ALND for patients with small volume nodal metastases who have been treated with neoadjuvant endocrine therapy?

D) Capacity for Organizational Change

30) How would you implement this change in your institution?

-Who are the stakeholders involved in making changes like this at your institution?

-Are there any perceived barriers to s