PROTOCOL

TITLE: Preoperative palbociclib in patients with DCIS of the breast that are candidates for surgery

PROTOCOL NUMBER: WI223281

EUDRACT NUMBER: 2014-000156-28

IND NUMBER: 137,811 IND EXEMPT

TEST PRODUCT: Palbociclib (Ibrance®)

INVESTIGATIONAL PRODUCT SUPPLIER: Pfizer Inc

FUNDING: Pfizer Inc

ClinicalTrials.gov IDENTIFIER: NCT03535506

PROTOCOL VERSION: 1.2

PROTOCOL VERSION DATE: 01/20/2022

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PROTOCOL SIGNATURE PAGE

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Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, all applicable regulations, ICH Good Clinical Practice (GCP) and Declaration of Helsinki.

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First Name, Last Name	Date, Signature

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PROTOCOL SYNOPSIS

Title	Preoperative palbociclib in patients with DCIS of the breast that are candidates for surgery
Study Drug	Palbociclib
Protocol Number	WI223281
Number of Patients	24
Length of Study	The total duration of the study is expected to be approximately 12 months.
Study Design	This is a feasibility study which will evaluate the effects of pre-operative treatment of DCIS of the breast with palbociclib. Patients with biopsy-proven DCIS are eligible for the study. There will be 2 independent and unrelated study groups of 12 patients each, for a total of 24 patients: (a) Group A, of *male or female* patients treated with palbociclib single agent (n=12); (b) Group B, untreated, of *male or female* patients who consented translational studies in blood, as well as diagnostic and definitive surgical specimen, but not the pre-operative treatment with palbociclib (n=12).
Primary Objectives	1) Feasibility 2) Preliminary evidence of DCIS response to palbociclib: Pathologic changes of breast tissue comparing paired biopsies before and after treatment (core vs definitive surgery) from each patient. a) Gross path, H&E changes, multiple biological markers (potentially including CDK4 and CDK6 expression, Cyclin D1 expression, P16 expression, Ki-67 proliferation, TFF1 expression, PCNA expression)
Secondary Objectives	1) Toxicities 2) Correlative science and tissue banking
Inclusion Criteria	**Inclusion Criteria for all patients (Groups A and B)** I.1 Signed informed consent obtained prior to any study specific assessments and procedures

	I.2 Age ≥18 years I.3 Premenopausal and postmenopausal women or men I.4 Current pathologic diagnosis of DCIS of the breast of any receptor status; a) History of previous DCIS allowed provided that the patient is currently off systemic risk-reduction endocrine therapy; b) History of previous invasive breast cancer adequately treated and that is currently in remission and unrelated to current DCIS (based on primary tumor location) is allowed as long as patient is currently off systemic therapy for that invasive cancer for at least 4 weeks prior to pre-treatment biopsy (diagnostic biopsy); c) Patients with multifocal or multicentric lesions are allowed, as long as one lesion is histologically confirmed DCIS and overall clinical AJCC Stage I. I.5 A formalin-fixed paraffin-embedded (FFPE) tumor tissue block from diagnostic biopsy must be transmitted to MedStar Georgetown University Hospital Pathology Department repository and confirmation of receipt must be available prior to enrollment. I.6 Positive Rb by immunohistochemistry in the DCIS component of the lesion a) Must be performed at CLIA-approved setting (for instance, MGUH) b) Rb staining will be considered positive when 1+ or above (in a scale of 0, 1+, 2+ or 3+) I.7 In the absence of histologic diagnosis of DCIS, patient may undergo fresh biopsy for eligibility, provided: a) This invasive procedure is not a Fine Needle Aspiration (FNA); AND b) This procedure is a core biopsy, stereotactic biopsy or incisional biopsy of the suspicious breast lesion; AND c) The primary lesion is not completely resected during the procedure. I.8 The patient is candidate for and is willing to receive definitive surgical therapy for DCIS I.9 ECOG performance status 0-1 (Appendix G: ECOG PS scale). I.10 Willingness to provide a sample of tissue collected at definitive surgery for research.

	Inclusion Criteria specific for patients enrolled on Group A I.11 Patients must be able and willing to swallow and retain oral medication I.12 Absolute neutrophil count (ANC) ≥ 1,500/mm3 I.13 Platelets ≥ 120,000/mm3 I.14 Hemoglobin ≥ 10g/dL I.15 Total serum bilirubin ≤ ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert's Syndrome. I.16 Aspartate amino transferase (AST or SGOT) and alanine amino transferase (ALT or SGPT) ≤ 1.5 × institutional ULN I.17 Serum creatinine within normal institutional limits or creatinine clearance ≥ 50 mL/min/1.73 m2 for patients with serum creatinine levels above institutional ULN. I.18 Pregnancy must be ruled out: a) Serum or urine pregnancy test must be negative within 14 days of treatment start in women of childbearing potential. b) Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before enrollment, or who have undergone tubal ligation, bilateral oophorectomy, total hysterectomy I.19 Willingness to undergo adequate contraception if childbearing potential a) Women of childbearing potential and male patients randomized into treatment Group A must use adequate contraception for the duration of protocol treatment and for 3 months after the last treatment with palbociclib if they are in Group A. b) Adequate contraception is defined as one highly effective form (i.e. abstinence, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusive cap with spermicidal foam / gel / film / cream / suppository). **There are no Inclusion Criteria specific for patients enrolled on Group B**

Exclusion Criteria	**Exclusion Criteria for all patients (Groups A and B)** E.1 Concurrent therapy with other Investigational Products. E.2 Invasive carcinoma present in the diagnostic biopsy • Microinvasion is allowed E.3 Uncontrolled intercurrent illness including (active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, pulmonary embolism in the past 6 months, or psychiatric illness/social situations that would limit compliance with study requirements). E.4 Unable to comply with study requirements E.5 Hormone therapies containing estrogen, progesterone, GnRH agonists and antagonists within 4 weeks from diagnostic biopsy. E.6 Therapy with any CDK inhibitor in the past 3 months **Exclusion Criteria Specific for patients enrolled on Group A** E.7 History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib E.8 Presence of a condition that would interfere with enteric absorption of palbociclib E.9 Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to enrollment • Breastfeeding must be discontinued prior to study entry (Group A only). E.10 Patients on combination antiretroviral therapy, i.e. those who are HIV+ (potential for pharmacokinetic interactions or increased immunosuppression with palbociclib). E.11 Patients receiving any medications or substances that are potent inhibitors or inducers of CYP3A isoenzymes within 7 days of enrollment or during participation on study (see Section 4.4.5 Prohibited Therapy for list of CYP3A inhibitors and inducers). E.12 Patients with clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis, etc. **There are no Exclusion Criteria specific for patients enrolled on Group B**

1. BACKGROUND

1.1 Background on Ductal Carcinoma in Situ (DCIS)

Ductal carcinoma in situ (DCIS) of the breast represents a heterogeneous group of neoplastic lesions confined to the breast ducts. In 2016, approximately 61,000 new cases of carcinoma in situ of the breast and 246,600 new cases of invasive breast cancer are expected to be diagnosed in American women[1]. With improvement in mammographic screening, the diagnosis of DCIS increased dramatically. DCIS now accounts for approximately 20-25% of detected breast carcinomas in screened populations[2]. Furthermore 40% of DCIS cases progress to invasive breast cancer if left untreated and the 20-year breast cancer-specific mortality rate following DCIS is 3.3%[3]. Therefore, the goal and challenge of therapy for DCIS is (1) to identify who needs treatment; and (2) to prevent the development of invasive breast cancer. Currently therapeutic approaches include surgery, radiation therapy, and adjuvant endocrine therapy. The key pathologic components of exam involve the following[4-7]:

- Nuclear grade (low, intermediate, or high).
- The size or extent of the lesion.
- The distance to the closest margin, including whether the margins were only focally or extensively involved.
- Specimen orientation to identify specific margins and allow for targeted re-excision if necessary.
- Estrogen and progesterone receptor status.

The most appropriate treatment for DCIS remains uncertain. One of the greatest challenges of today's DCIS treatment is minimizing overtreatment and undertreatment of the disease[8]. Prognostic classifications have been created in an attempt to guide therapy development, planning and delivery. These classifications typically include the above mentioned pathologic features as well as patient age[9,10]. Unfortunately, the classifications based on clinicopathologic characteristics and standard biomarkers are still imprecise in stratifying risk and potential benefit with available interventions including surgery, radiation and endocrine therapy[11]. The emergence of new efficacious and safe targeted therapies in oncology allows the design of trials that could help identifying unique populations of patients candidates for the emerging intervention [12,13].

DCIS management: At the present time, for patients treated with mastectomy no additional therapy is typically recommended. On the other hand, patients treated with lumpectomy are offered post-lumpectomy radiation and, if estrogen and progesterone receptors are present, risk reduction endocrine therapy for 5 years. The decision between mastectomy or lumpectomy, radiation and tamoxifen for treatment of DCIS is typically difficult for patients. Mastectomy provides overly aggressive treatment for many women[1]. After mastectomy, disease recurrence rate is estimated at approximately 2%[14-16]. Unfortunately, when recurrent after mastectomy, it carries a high mortality rate for those who do relapse[16]. The risk of distant metastasis seems to be significantly higher in high grade DCIS when compared to low grade DCIS[17]. In multiple studies, younger age was found to be an independent risk factor for recurrence in multivariate analysis[16,18]. In addition, unexpected invasive carcinoma is found in 15-25% of mastectomies performed for DCIS[19]. When invasive carcinoma is present at definitive surgery, treatment plan is updated and focuses on the higher risk lesion, involving a multidisciplinary approach.

Approximately 70% of women with newly diagnosed DCIS are managed with breast conserving surgery[20]. Lumpectomy has less morbidity but this is associated with a higher risk of local recurrence,

even when combined with radiation therapy, than mastectomy alone. A recent report from a retrospective study of approximately 32,000 patients in the Surveillance, Epidemiology, and End Results (SEER) database treated with lumpectomy for DCIS indicated that adjuvant radiation was associated with improved breast specific survival for patients with high nuclear grade, younger age, or larger tumor size[21]. A long-term follow-up report from NSABP B–17 and B–24 randomized clinical trials for DCIS revealed that after 15 years, invasive ipsilateral breast tumor recurrence occurred in 19.4% of patients who received lumpectomy alone compared with 8.5% of patients who received lumpectomy, radiation and tamoxifen[22]. The presence of invasive recurrence was associated with an increase in mortality risk, but recurrence of DCIS was not. The overall mortality was low in patients who underwent lumpectomy. Among women diagnosed with DCIS, the risk of developing contralateral breast cancer or DCIS is approximately 3 to 10 percent[23-25]. In a recent retrospective study 108,196 cases of DCIS were analyzed with extensive follow-up data, revealing that aggressive treatment did not reduce the number of breast cancer associated deaths, and highlighting the need for novel treatment strategies[26]. In that report, occurrence of invasive cancer after DCIS substantially increased the risk of cancer-related death.

Tailored treatment for DCIS: Attempts have been made to de-escalate care for patients with very low risk DCIS. To define a population in which radiation therapy could be omitted after lumpectomy, the Eastern Cooperative Oncology Group (E5194) investigated lumpectomy without radiation in selected patients (<2.5 cm of low- to intermediate-grade DCIS or <1.0 cm for high-grade DCIS)[27]. Median tumor size was only 6 mm. The 12-year local recurrence rate for low– or intermediate–grade, or for high-grade DCIS was 14.4% and 24.6%, respectively. These results support the impression that higher grade lesions are associated with higher risk of recurrence. A more recent approach to help determining risk for better treatment planning involves the use of gene expression analysis. The Oncotype DX DCIS recurrence score has also been studied as a tool for identification of patients for whom post lumpectomy radiation could be reasonably omitted[28]. However, data regarding its suitability are still preliminary[1], and again the assay does not identify clearly patients who will develop recurrence even treated with maximum current available treatment. Risk of recurrence after lumpectomy varied between 7.5% and 20.5%, according to assay score and use of radiation[29].

Endocrine risk reduction therapy with tamoxifen, raloxifene or aromatase inhibitors (AIs) is recommended for women with hormone positive DCIS. While tamoxifen has been shown to reduce the risk of breast cancer by 49% in women with DCIS, long-term treatment with tamoxifen does carry multiple risks, including increased risk of endometrial cancer and venous thrombosis, which are higher for women over 50yrs. Raloxifene is often better tolerated than tamoxifen; however, it appears to be less efficacious for prevention of invasive breast cancer in long-term follow-up[30]. AIs have recently been added to the NCCN guidelines as a risk-reduction agent. In the MAP3 trial[31], exemestane decreased the relative risk of invasive breast cancer by 65% over 3 years but AIs carry their own risks with long-term use (i.e., osteoporosis, joint pain).

Better risk stratification and more effective and tolerable treatments are needed to help prevent DCIS recurrence or progression of these in situ lesions into more invasive cancers. Ongoing trials continue to evaluate lumpectomy, radiation and endocrine therapy with tamoxifen or with an AI. This is the case of NSABP B-35 and IBIS II (anastrozole or tamoxifen) and CALGB 40903 (letrozole). NSABP B-43 on the other hands evaluates the potential efficacy of trastuzumab for HER2 positive DCIS. There is no approved systemic risk-reducing treatment for ER/PR negative DCIS.

Based on the above-mentioned statistics we estimate approximately 43,000 women would be treated with lumpectomy for DCIS each year in this country. If 15-25% of them are expected to experience recurrence with currently available therapies, this would represent approximately 6,500 to 10,750 women who could have benefitted from different, newer treatments, if available, every year.

The challenges are to identify, at the time of diagnosis, the patients more likely to develop recurrence and subsequent morbidity, and to develop effective therapies that could prevent morbidity from recurrence in this higher risk population.

1.2 Background on Palbociclib

1.2.1 Cdk4, Cdk6, Rb

Deregulation of the cell-cycle machinery is a fundamental hallmark of cancer progression and a common feature in carcinogenesis[32,33]. Cyclin-dependent kinases Cdk4 or Cdk6, regulate events in the G1 phase of the cell cycle and contribute to the phosphorylation of the retinoblastoma gene product (Rb). However, in cells in which the function of Rb has been compromised, Cdk4 and Cdk6 are not associated with D cyclins, but rather with p16. Rb negative cells express high levels of p16, competing with D cyclins for binding to Cdk4 and Cdk6, preventing the formation of active complexes[34]. In the cell cycle, during the progression through G1, growth signals allow cyclin D to complex with either Cdk4 or Cdk6. This process facilitates the addition of phosphate groups to Rb. As the cell progresses from G1 to S, cyclin E complexes with Cdk2 and hyperphosphorylates Rb, with release of bound E2F. This E2F activates S-phase genes allowing cell cycle progression[35]. In tumors with intact Rb, the process of Rb phosphorylation and inactivation necessary to facilitate cell division is rate limited by cyclin D1 levels[36].

1.2.2 Palbociclib

Palbociclib is a new, oral, highly specific small-molecule inhibitor of Cdk4 and Cdk6. Palbociclib potently, equally and selectively inhibits both Cdk4 and Cdk6–cyclin D1 kinase activity[37]. Its efficacy has been demonstrated in a number of Rb proficient human cancer cells, including breast cancer. In vitro studies have demonstrated high activity in hormone receptor positive breast cancer cell lines, which are the most likely to have an intact Rb pathway, especially when added to endocrine therapies like tamoxifen and letrozole. In addition, a study in which 18 TNBC cell lines were screened for sensitivity to palbocicilb in long-term clonogenic assays revealed sensitivity of the luminal-androgen (LAR) and mesenchymal-stem like (MSL) triple negative subsets, in particular in association with expression of androgen receptor ($p = 0.0013$), and with the absence/or low levels of cyclin E1 ($p = 0.01$)[38].

1.2.3 Palbociclib in Advanced HER2-negative Breast Cancer

Palbociclib was recently approved by the FDA for use in metastatic hormone receptor positive breast cancer based on the results of the PALOMA-1/TRIO-18 study which found a significant increase in progression-free survival from 10.2 months for letrozole alone compared to 20.2 months for palbociclib combined with letrozole[39]. The PALOMA-3 trial is a phase III clinical trial demonstrating that among women with hormone receptor positive metastatic breast cancer, palbociclib combined with fulvestrant resulted in longer progression-free survival (9.2 months) than fulvestrant alone (3.8 months; $p < .001$)[40].

1.2.4 Palbociclib in Early HER2-negative Breast Cancer

Due to the success of palbociclib when combined with endocrine therapy in the metastatic setting, there is now growing interest in the potential use of this drug in earlier disease states. The FB-11/PALLET trial is an ongoing phase II trial where women with early hormone receptor positive breast cancer receive neoadjuvant palbociclib +/- letrozole (NCT02296801). In August 2015 The Alliance Foundation Trials, LLC (AFT), the Austrian Breast & Colorectal Cancer Study Group (ABCSG), and Pfizer Inc. announced the launch of the Palbociclib Collaborative Adjuvant Study, or PALLAS (NCT02513394). This global Phase 3 clinical trial for patients with early-stage breast cancer is being conducted in conjunction with Breast International Group (BIG), German Breast Group (GBG), National Surgical Adjuvant Breast and Bowel Project (NSABP), and PrECOG, LLC (PrECOG). The PALLAS trial is evaluating whether the addition of palbociclib, to standard therapy will improve disease-free survival and prevent the disease from recurring. Patients treated in this study have hormone receptor-positive (HR+), HER2 negative breast cancer treated with curative intent by surgery.

1.2.5 Palbociclib clinical toxicity and safety

Palbociclib 125mg PO daily continuously for 21 days followed by 7-day rest period in combination with endocrine therapy is the approved schedule by FDA for treatment of patients with metastatic HR+HER2- breast cancer. In the studies leading to FDA approval, Palbociclib was used until disease progression or unacceptable toxicity (median duration of palbociclib therapy > 12 months). Therefore, the schedule used to treat patients with metastatic disease includes higher dose, longer exposure in each cycle and longer length of treatment overall than those proposed in the current study for DCIS patients (a single cycle of Palbociclib 100mg daily for 12 days).

The clinical safety of Palbociclib (125 mg/day) plus Letrozole (2.5 mg/day) versus Letrozole alone was clinically evaluated in 160 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of treatment in a phase II study [39]. Overall this treatment combination is considered very well tolerated, allowing patients to carry on with personal and professional daily activities. Palbociclib doubled PFS when added to Letrozole, as compared to Letrozole alone. Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving Palbociclib plus Letrozole. Permanent discontinuation associated with an adverse reaction occurred in 7 of 83 (8%) patients receiving Palbociclib plus Letrozole and in 2 of 77 (3%) patients receiving letrozole alone. Adverse reactions leading to discontinuation for those patients receiving Palbociclib plus Letrozole included neutropenia (6%), asthenia (1%), and fatigue (1%). The most common adverse reactions (≥10%) of any grade reported in patients in the Palbociclib plus Letrozole arm were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. The most frequently reported serious adverse reactions in patients receiving Palbociclib plus Letrozole were pulmonary embolism (3 of 83; 4%) and diarrhea (2 of 83; 2%). An increased incidence of infections was observed in the Palbociclib plus Letrozole arm (55%) compared to the letrozole alone arm (34%). Febrile neutropenia has been reported in the Palbociclib clinical program, although no cases were observed in that study. Grade ≥3 neutropenia was managed in that study by dose reductions and/or dose delay, or

temporary discontinuation. Adverse reactions (≥10%) reported in patients who received Palbociclib plus Letrozole or Letrozole alone are listed in Table 1.

Table 1. Adverse Reactions (>=10%) of Letrozole +/- Palbociclib (PALOMA trial) [39]

Adverse Reaction	IBRANCE plus Letrozole (N=83)			Letrozole Alone (N=77)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
URI*	31	1	0	18	0	0
Blood and lymphatic system disorders						
Neutropenia	75	48	6	5	1	0
Leukopenia	43	19	0	3	0	0
Anemia	35	5	1	7	1	0
Thrombocytopenia	17	2	0	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	7	0	0
Nervous system disorders						
Peripheral neuropathy†	13	0	0	5	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11	0	0	1	0	0
Gastrointestinal disorders						
Stomatitis‡	25	0	0	7	1	0
Nausea	25	2	0	13	1	0
Diarrhea	21	4	0	10	0	0
Vomiting	15	0	0	4	1	0
Skin and subcutaneous tissue disorders						
Alopecia	22§	N/A	N/A	3¶	N/A	N/A
General disorders and administration site conditions						
Fatigue	41	2	2	23	1	0

The safety of Palbociclib (125 mg/day) plus Fulvestrant (500 mg) versus placebo plus Fulvestrant was evaluated in another clinical trial of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment [41]. Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving Palbociclib plus fulvestrant. Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving Palbociclib plus fulvestrant, and in 6 of 172 (3%) patients receiving placebo plus fulvestrant. Adverse reactions leading to discontinuation for those patients receiving Palbociclib plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%). The most common adverse reactions (≥10%) of any grade reported in patients in the Palbociclib plus fulvestrant arm were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, vomiting, alopecia, rash, decreased

appetite, and pyrexia. The most frequently reported serious adverse reactions in patients receiving Palbociclib plus fulvestrant were infections (3%), pyrexia (1%), neutropenia (1%), and pulmonary embolism (1%). Adverse reactions reported in patients who received Palbociclib plus fulvestrant or placebo plus fulvestrant in this study are listed in Table 2.

Table 2. Adverse Reactions (>=10%) of Fulvestrant +/- Palbociclib (PALOMA3 trial) [41]

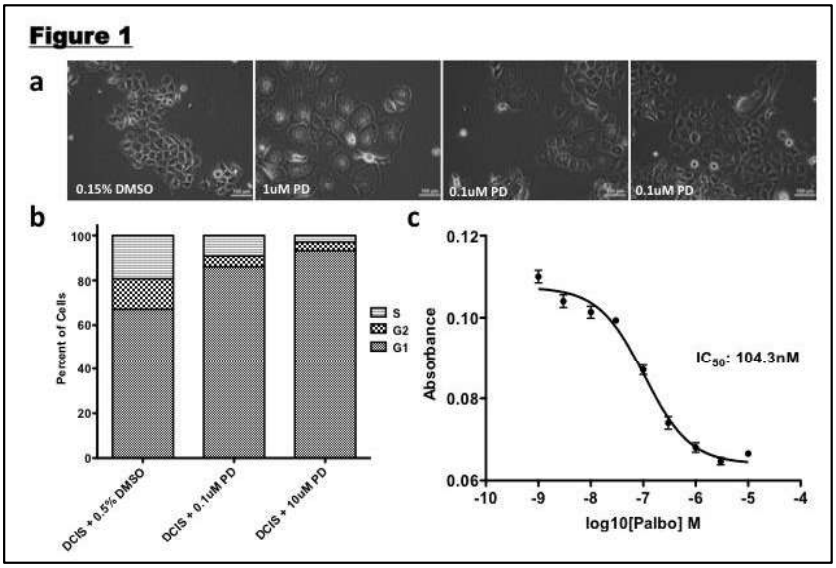
Adverse Reaction	IBRANCE plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections*	47	3	1	31	3	0
Blood and lymphatic system disorders						
Febrile neutropenia	1	1	0	1	0	1
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	3	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Eye disorders						
Vision blurred	6	0	0	2	0	0
Lacrimation increased	6	0	0	1	0	0
Dry eye	4	0	0	2	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Nervous system disorders						
Headache	26	1	0	20	0	0
Dysgeusia	7	0	0	3	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	7	0	0	2	0	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0

In a phase I study [42], palbociclib related neutropenia and thrombocytopenia occurred around day 21, the end of 21-day period of continuous PO daily dose in a 28-day cycle. In cycle 1, rebound of both ANC and platelet levels were observed during the off-drug period that continued up to day 8 of the following dosing cycle.

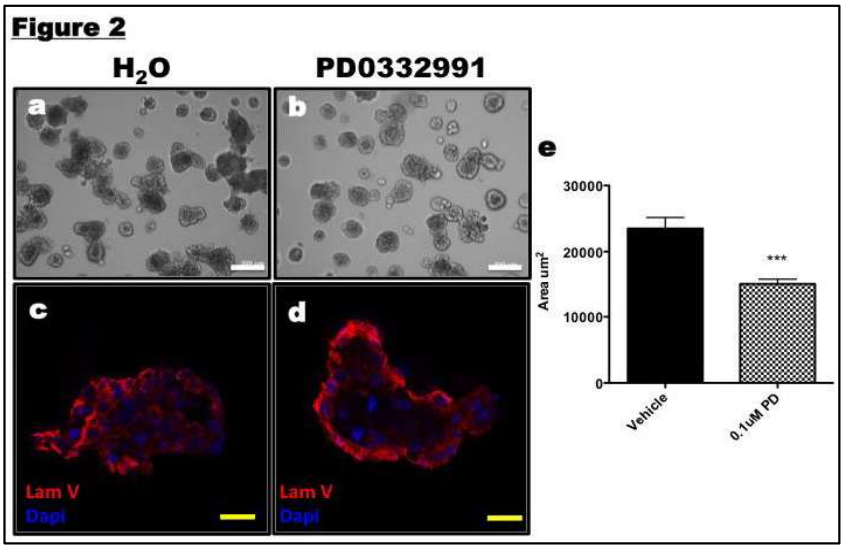
1.3 Study Rationale

1.3.1 Preclinical experience on CDK4/6 inhibition and DCIS

Loss of the retinoblastoma tumor suppressor pathway (Rb) is one of the strongest markers of DCIS recurrence and progression. Preclinical studies support the development of Cdk 4/6 inhibitors in DCIS. Cdk4 and Cdk6 are very important in cellular proliferation; they phosphorylate Rb and initiate transition from the G1 phase to the S phase in the cell cycle. Inhibition of Cdk4 and Cdk6 activity in an Rb-dependent manner prevents the development of invasion lesions[43]. Furthermore, immortal mammary epithelial cell lines with Rb knockout lead to invasive lesions in xenograft assays but Rb proficient parental cells lead to DCIS-like lesions[43].



In our hands, the well-established MCF-DCIS in vitro model gives well defined DCIS lesions when implanted subcutaneously in animals. These lesions progress to invasive disease within 3-5 weeks in this model[44,45]. Pathologic features and gene expression pattern of MCF-DCIS mimics that of human DCIS lesions[46]. The ductal lesions that develop after 3 weeks implantation of MCF-DCIS cells resemble high grade comedo DCIS and both the luminal and myoepithelial cell layers of the DCIS lesions are derived from the progenitor MCF-DCIS cells[45,47]. We determined that palbociclib can inhibit MCF-DCIS proliferation in vitro (**Fig 1**). The IC_{50} was approximately 100 nM, at which concentration there was significant change in morphology of the cells. We also observed a significant decrease in Cdk2 and PCNA expression in the cells with low



doses of palbociclib treatment. In Matrigel™ model, MCF-DCIS cells grow into multiacinar structures (**Fig 2**). When exposed to palbociclib 0.1µM for 7 days, there was significant change in laminin V distribution to the periphery of the acini and a more normal steroid acinar structure was observed (**Fig 2d**).

In previous xenograft studies at our center, with an Rb-dependent mammary gland dysplasia mouse model *Tet-op-TAg*$^{MMTV\text{-}tTA}$, 10 days of exposure to Palbociclib significantly reduced the percentage of hyperplastic and dysplastic ductal structures [58% vs. 7%; p<0.01] and significantly increased the percentage of normal-like structures [9% vs. 62%; p<0.01] as compared with untreated controls[48]. Cyclin D1, Cdk6, Cdk4, phospho pRb, DP-1, and E2F-1 were significantly reduced and p21 and p27 significantly increased as compared with untreated controls [all p<0.05]. Our preclinical results indicate that palbociclib may prevent maintenance of DCIS and its malignant progression.

Interrupting cancer development by inducing resolution of precancerous lesions is an established cancer prevention goal[49]. Based on preclinical DCIS information and on clinical experience with palbociclib for patients with metastatic cancer, the concept of developing palbociclib as potential chemoprevention agent is felt to be very promising.

1.3.2 Palbociclib as potential treatment for DCIS

Nothing is known about the clinical or biological activity of palbociclib in human DCIS or early stage breast cancer. This project is designed to understand and describe palbociclib activity in humans, in particular in pre-invasive lesions such as DCIS, and to provide critical preliminary data supportive of future efficacy studies. For the design of efficacy clinical studies that would lead to potential new label indication, preliminary human data must be indicative of its potential clinical usefulness for this population of patients. That is the reason for the current study: to generate supportive information in humans that will allow the design of a larger efficacy study.

This study will validate the incorporation of an informative preoperative short treatment phase as potential strategy to select DCIS patients, a crucial step for the development of treatment with palbociclib in this condition.

Palbociclib as single agent: The current study will represent a unique opportunity to evaluate the potential effect of single agent palbociclib on non-invasive breast lesions. Preclinical models suggest that in DCIS, palbociclib single agent may be sufficient. Apart from strong evidence supporting the activity of palbociclib combined with endocrine therapy, multiple TNBC cell lines where endocrine therapy would have no role have been screened for sensitivity to palbocicilb[38], revealing sensitivity of the luminal-androgen (LAR) and mesenchymal-stem like (MSL) triple negative subsets. In addition, palbociclib was active in the single agent phase IA escalation study A548100152, where 74 heavily pretreated patients with various types of solid tumors or lymphomas, including 6 patients with breast cancer, were treated. There was 35% SD for at least 2 cycles with one breast cancer patient receiving 50 mg QD with SD lasting longer than 10 cycles. Another reason to study single agent palbociclib in DCIS is that endocrine therapy is the only systemic treatment currently approved for DCIS. Endocrine therapy has well known potential side effects that may interfere significantly with quality of life of patients, including hot flashes, fluid retention, vaginal symptoms, thromboembolic complications, cataract, dyslipidemia, arthralgia, osteoporosis and uterine cancer [50,51]. If palbociclib has biologic activity in DCIS as a single agent, this could represent a change in paradigm.

2. OBJECTIVES AND OUTCOME MEASURES

2.1 Hypothesis

The null hypothesis is that patients with DCIS of the breast who are treated with 12 days of pre-operative palbociclib will have no change in the gross DCIS pathology, microscopic morphology on H&E, or expression of phospho-Rb, Ki-67 proliferation, and multiple other biological markers of their cancer.

2.2 Objectives

2.2.1 Primary Objectives

- Feasibility
- Preliminary evidence of DCIS response to palbociclib: Pathologic changes of breast tissue comparing paired biopsies before and after treatment (core vs definitive surgery) from each patient.
    - Gross path, H&E changes, multiple biological markers (potentially including CDK4 and CDK6 expression, Cyclin D1 expression, P16 expression, Ki-67 proliferation, TFF1 expression, PCNA expression)

2.2.2 Secondary Objectives

- Toxicities
- Correlative science and tissue banking

2.3 Outcome Measures

Feasibility: the approach will be considered feasible if more than 50% of the enrolled patients are treated and followed within protocol rules, if collected samples are suitable for studies, and if pathologic changes are detectable when comparing diagnostic and surgical specimens, or treated and untreated specimens. In Group A, patients will be treated with palbociclib alone, providing the opportunity to address if proposing this kind of treatment for these patients is feasible. Obtaining human data and feasibility data would be key for designing efficacy/definitive studies of palbociclib in DCIS.

Pathology: we will perform descriptive analysis of microscopic and molecular changes upon exposure to palbociclib. Biological markers will be tested by immune histochemistry (IHC). Source for comparison will be pretreatment versus post-treatment paired samples. This study will represent an opportunity to describe potential pathological changes triggered by palbociclib as a single agent in DCIS.

Toxicity: will be evaluated by CTCAE. There is no plan to compare Groups A and B regarding efficacy or toxicity. Toxicity will be descriptive for each treatment group, independently.

Correlative science: Will be performed at Lombardi Comprehensive Cancer Center. Preliminary data for this proposal was obtained using a well-established model of DCIS progression with the human MCF-DCIS cell line[45,47]. Proposed translational components are currently routinely done at LCCC. There is no plan to compare Groups A and B regarding translational changes. Paired samples (pre- and post-systemic therapy) will be compared within the respective Group. **DCIS Sample #1** is the core biopsy

done for diagnosis, **DCIS Sample #2** is collected at definitive surgery; both collected from the same patient (paired).

3. STUDY DESIGN

3.1 Description of Study

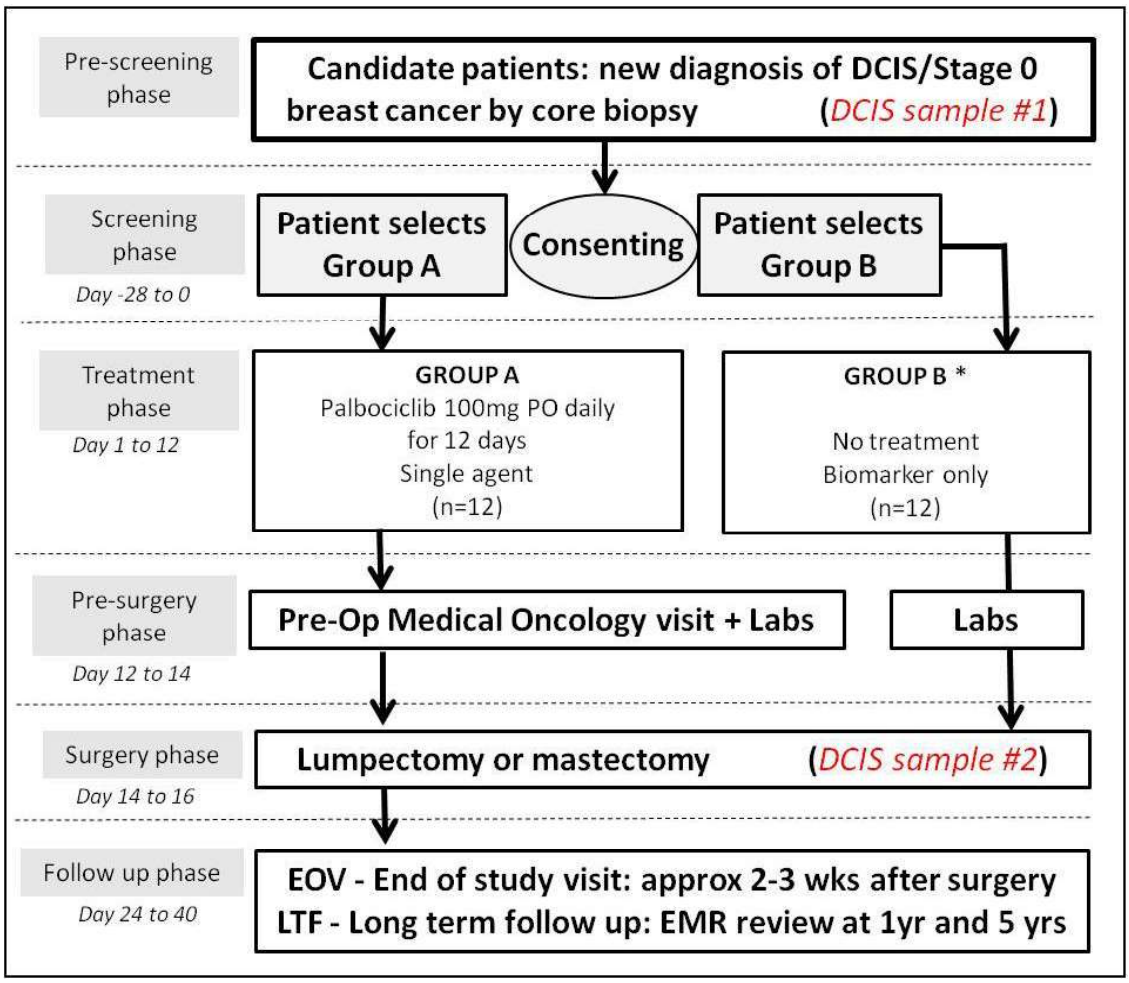
3.1.1 Overview of Study Design

This is a feasibility study which will evaluate the pre-operative treatment of DCIS of the breast with palbociclib. Patients with biopsy-proven DCIS are eligible for the study.

There will be 2 independent and unrelated study groups of 12 patients each, for a total of 24 patients:

(a) Group A, of *male or female* patients treated with palbociclib single agent (n=12);
(b) Group B, untreated, of *male or female* patients who consented translational studies in blood, as well as diagnostic and definitive surgical specimen, but not the pre-operative treatment with palbociclib (n=12).

Figure 3: Study schema



** Please refer to Timing of Surgery item below for details on scheduling for Group B.*

Patients will be offered participation in the study at the diagnosis of DCIS (confirmed by pathology). Patients could consent biomarker and treatment (Group A) or biomarker-study only (Group B) activities. Once the patient is consented, archival tissue from the diagnostic biopsy will be obtained during screening and used for research in both Groups A and B. Positive Rb by immunohistochemistry in the DCIS component of the lesion will be required for participation on both Groups A and B. Patients consenting study participation will be referred to Medical Oncology clinic and undergo screening. After successful screening, patients enrolled on Group A will be treated preoperatively with palbociclib. **There will be no randomization**. The assignment to Group A or B is based on patient's choice. All patients consenting treatment on Group A will receive palbociclib alone. Since some patients may consent tissue collection, but not preoperative palbociclib treatment, Group B was created to acquire information about contemporary patients receiving biopsy followed by definitive surgery. This approach was first described by Stearns and Davidson[52].

Choice of histology: a core biopsy showing DCIS-only will not rule out invasive disease. In some instances, invasive disease is found at definitive surgery. Since the proposed treatment will happen between diagnostic biopsy and definitive surgery, it is not practical to exclude from analysis patients

that are found to have invasive disease at definitive surgery that was concomitant with DCIS. Information about the invasive component will be collected if present, but the purpose of the current project is to describe palbociclib effects on the DCIS component. Likewise, if other concomitant lesions are detected at final pathology from definitive surgery, i.e. lobular neoplasia, atypical hyperplasia, papilloma, etc, pertinent data will be collected. However, this study will be focused on the effects of palbociclib on the DCIS component of lesions. Since hormonal receptors in DCIS are typically available only at pathologic specimen from definitive surgery, ER or PR status will not be used for patient selection in this feasibility study. Information on ER and PR status will be collected from the pathology report of definitive surgery.

Rb screening: Diagnostic biopsies of participating patients will be tested for Rb expression by immunohistochemistry during trial Screening Phase. The expression of Rb in DCIS lesions is expected in greater than 80% of the cases[53]. *We estimate 30 patients* will need to be screened with Rb staining of diagnostic biopsies to complete enrollment. The turnaround time of this test at MedStar Georgetown University Hospital when pathology specimen is located at main laboratory is 48-72hr and therefore considered feasible as screening procedure. This is based on previous extensive experience at our institution with a phase I clinical trial that is ongoing (NCT01522989)[54]. The population will therefore be enriched to increase the likelihood of benefit from this therapy through Rb status evaluation by immunohistochemistry (IHC) at study entry. Rb staining will be considered positive when 1+ or above (in a scale of 0, 1+, 2+ or 3+).

Timing of definitive surgery: All enrolled patients will undergo definitive surgery (mastectomy or lumpectomy).

Group A:

First day of palbociclib treatment will be called Day #1 on study. Last day of palbociclib treatment will be called Study Day #12. Definitive surgery will be performed after end of palbociclib in Group A, on Study Day #15 +/-1. The short period between end of palbociclib and surgery date was selected observing safety and translational data from patients with invasive ductal carcinoma treated with higher dose and longer period of palbociclib in the neoadjuvant setting. A long wash out period without the drug prior to surgery (2-4 weeks) is not desirable since it may be associated with rebound on Ki67 in patients receiving neoadjuvant palbociclib for invasive ductal carcinoma[55]. In 8 patients receiving additional palbociclib 125 mg QD for 12 days until the day prior to surgery, recovery of Ki67 in tissue was diminished[55]. This study also showed that it was safe to proceed with immediate surgery after the palbociclib treatment specified above.

In the current study, the starting date of treatment with Palbociclib for Group A patients will be determined by the surgery date schedule. A maximum period of 4 weeks between initial biopsy and definitive surgery is estimated for patients enrolled to treatment Group A. In case of cytopenias, surgery will be postponed for 7 days (**please refer to session 5.1.3 Management of Specific Adverse Events, for details**). This interval was felt to be acceptable and in line with current practice out of clinical trials. Minimum length of time from enrollment to definitive surgery on treatment Group A is estimated 18 days (Eligibility verification, Rb-testing, Palbociclib dispensation, Palbociclib treatment for 12 days and definitive surgery after stopping treatment).

Group B:

There is no preoperative palbociclib treatment in Group B. Accounting for healing process after diagnostic biopsy, consenting process, Rb screening and to prevent excessive delays since original diagnosis, we recommend that definitive surgery occurs between 5 and 42 days since original diagnostic biopsy.

Collection of tissue at definitive surgery (sample #2): A certified pathologist will be responsible for tissue handling and destination to research. Unfortunately, performing a research-only core at surgery is not felt to be practical in patients with diagnosis of DCIS, since one of the key components of pathologic exam is to rule out invasive component. Therefore, an additional core at surgery is not felt to be safe for patients. Tissue will be collected for translational studies based on certified pathologist examination of material and without compromise of definitive diagnosis. There is a possibility that at definitive surgery invasive lesions are detected. We will describe the same parameters for DCIS lesions and for invasive lesions. Invasive component histologic abnormalities description will be purely exploratory. The focus of this study is DCIS. Pathologist will fill out a form confirming collection of sample for the trial (Appendix L)

Follow up period: Patients will be followed at the postoperative period in the outpatient setting, at which point any additional systemic treatment for DCIS or invasive breast cancer will be discussed. The End of Study visit will occur approximately 2 to 3 weeks after surgery. The Informed Consent form will contain terminology asking patients for permission for the researchers to review the medical chart at 1 year and at 5 years from enrollment to collect additional clinical information about medical history, disease status and treatments.

The study procedures are summarized in Appendix A.

The study schema is presented in Appendix B.

The calendar template for treatment and visits timeline planning based on surgery date for patients enrolled on treatment Group A (Palbociclib) is presented in Appendix C.

The Enrollment Process to Treatment Overview is presented in Appendix D.

3.2 End of Treatment

The total duration of Palbociclib treatment is 12 days, beginning any time after enrollment. Definitive surgery will occur 3 (+/- 1day) after end of palbociclib treatment, on study day #15 +/- 1 day. The end of treatment visit will occur 32 (+/- 8 days) after surgery. Unless a patient discontinues treatment early or experiences treatment delays, this would result in 24-40 days on trial. Any premature, permanent termination of IP treatment is referred to as “Early End of IP-treatment”. “End of IP treatment per protocol” means Palbociclib treatment ended after 12 days.

Any one of the following criteria will be reason to stop IP-treatment before 12 days:

- General or specific changes in the participant's condition render the participant not a candidate for further treatment in the opinion of the treating investigator
- Unacceptable toxicity or unacceptable adherence to palbociclib.
- Patient withdraws consent

3.3 End of Study

The study ends when all enrolled patients complete trial procedures.

End of study is the date when the last patient has completed their end of study visit, all data have been collected, and all queries have been resolved.

The study may be terminated in case of excessive toxicity (please refer to section "**4.6.2 Study Termination**") or if deemed not feasible (section "**2.3 Outcome Measures; feasibility**").

3.3.1 End of Study Visit

Patient's end of study visit is the last formal study visit, or last formal contact or an unscheduled study visit in case of early withdrawal from all Phases of the study for treatment and follow-up.

3.3.2 Managing Patients Who Never Received Protocol Treatment

Patients who never received definitive surgery will be substituted.
Patients who are enrolled to the trial on Group A, but never received Palbociclib will be substituted.

3.3.3 Patients Lost to Follow Up

During the duration of the study, sites will be expected to continue efforts to contact all enrolled patients as well as regularly consult publicly available information to ascertain vital status of the patient. After End of study visit, patients will allow long term follow up through medical records review for medical history, additional treatments, disease and survival status, as well as a telephone call at 1yr and at 5yrs from definitive surgery. In cases where sites cannot successfully contact a patient and is not able to receive appropriate publicly available information for greater than two years, the patient will be noted as lost to follow up.

3.4 Rationale for Study Design

3.4.1 Rationale for Test Product Dosage (Palbociclib)

Choice of palbociclib dose: A smaller than approved dose was selected for safety concerns, minimizing the risk of neutropenia in the pre-operative period. We expect this dose to be efficacious against the early stage lesions from enrolled patients based on described experience in palbociclib study A5481001[42]. In that single agent escalation study plasma pharmacokinetics parameters had low variability with a small dose-dependent increase in exposure over the dose range of 100 to 150 mg, based on Cmax and AUC from 0 to 10 hours. The dose limiting toxicity was neutropenia. During cycle #1 the more severe neutropenia reported at 100mg daily was graded as 2 (CTCAE). With 125mg daily, neutropenia reached grade 3.

A) Group A (Palbociclib treatment)

Group A will receive palbociclib 100mg by mouth daily for 12 days prior to definitive surgery.
Palbociclib will be provided by Pfizer.

B) Group B (Observation)

Group B will receive no preoperative treatment.

3.4.2 Rationale for Choice of Regimen

Choice of palbociclib treatment duration: Typical interval between diagnostic biopsy and definitive surgery in DCIS varies from 7-28 days. This is the interval in which enrollment, screening and treatment will take place in this study. In the phase IA palbociclib escalation study A5481001[42], patients were treated for 2 on/1 off weeks or for 3 on/1 off weeks. In the 3 on/1 off group, neutropenia and thrombocytopenia nadir occurred between days 15 and 22 of uninterrupted treatment. In another phase I trial of palbociclib in combination with chemotherapy, metastatic tumor biopsies performed after 7 days of palbociclib single agent demonstrated histologic changes in comparison to pretreatment biopsy in some patients (NCT01522989)[54]. In a neoadjuvant trial of palbociclib and anastrozole presented at SABCS 2015, 8 patients with invasive breast cancer received a delayed course of palbociclib 125 mg QD for 10 to 12 days until the day prior to surgery, to address Ki67 changes in tissue[55]. There were no delays on surgery date due to toxicity. Therefore, we decided to treat patients for 12 days to ensure safe and adequate exposure to drug.

4. MATERIALS AND METHODS

4.1 Patients

4.1.1 Inclusion Criteria

Inclusion criteria for all patients (Groups A and B):

Inclusion Criteria for all patients (Groups A and B)	
I.1	Signed informed consent obtained prior to any study specific assessments and procedures
I.2	Age ≥18 years
I.3	Premenopausal and postmenopausal women, or men
I.4	Current pathologic diagnosis of DCIS of the breast of any receptor status; History of previous DCIS allowed provided that the patient is currently off systemic risk-reduction endocrine therapy; History of previous invasive breast cancer adequately treated and that is currently in remission and unrelated to current DCIS (based on primary tumor location) is allowed as long as patient is currently off systemic therapy for that invasive cancer for at least 4 weeks prior to pre-treatment biopsy (diagnostic biopsy); Patients with multifocal or multicentric lesions are allowed, as long as at least one lesion

	is histologically confirmed DCIS and overall clinical AJCC Stage 0 or I.
I.5	A formalin-fixed paraffin-embedded (FFPE) tumor tissue block from diagnostic biopsy must be transmitted to MedStar Georgetown University Hospital Pathology Department repository and confirmation of receipt must be available prior to enrollment.
I.6	Positive Rb by immunohistochemistry in the DCIS component of the lesion Must be performed at CLIA-approved setting (for instance, MGUH) Rb staining will be considered positive when 1+ or above (in a scale of 0, 1+, 2+ or 3+)
I.7	In the absence of histologic diagnosis of DCIS, patient may undergo fresh biopsy for eligibility, provided: This invasive procedure is not a Fine Needle Aspiration (FNA); AND This procedure is a core biopsy, stereotactic biopsy or incisional biopsy of the suspicious breast lesion; AND The primary lesion is not completely resected during the procedure.
I.8	The patient is candidate for and is willing to receive definitive surgical therapy for DCIS
I.9	ECOG performance status 0-1 (Appendix G: ECOG PS scale).
I.10	Willingness to provide a sample of tissue collected at definitive surgery for research.

Inclusion criteria specific to treatment Group A:

	Inclusion Criteria specific for patients enrolled on Group A
I.11	Patients must be able and willing to swallow and retain oral medication
I.12	Absolute neutrophil count (ANC) ≥ 1,500/mm^3
I.13	Platelets ≥ 120,000/mm^3
I.14	Hemoglobin ≥ 10g/dL
I.15	Total serum bilirubin ≤ ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert's Syndrome.
I.16	Aspartate amino transferase (AST or SGOT) and alanine amino transferase (ALT or SGPT)

	≤ 1.5 × institutional ULN
I.17	Serum creatinine within normal institutional limits or creatinine clearance ≥ 50 mL/min/1.73 m^2 for patients with serum creatinine levels above institutional ULN.
I.18	Pregnancy must be ruled out: Serum or urine pregnancy test must be negative within 14 days of treatment start in women of childbearing potential. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before enrollment, or who have undergone tubal ligation, bilateral oophorectomy, total hysterectomy
I.19	Willingness to undergo adequate contraception if childbearing potential Women of childbearing potential and male patients randomized into treatment Group A must use adequate contraception for the duration of protocol treatment and for 3 months after the last treatment with palbociclib if they are in Group A. Adequate contraception is defined as one highly effective form (i.e. abstinence, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusive cap with spermicidal foam / gel / film / cream / suppository).

There will be no specific criteria for Group B since this is a biorepository only group.

4.1.2 Exclusion Criteria

Exclusion criteria for all patients (Groups A and B):

	Exclusion Criteria for all patients (Groups A and B)
E.1	Concurrent therapy with other Investigational Products.
E.2	Invasive carcinoma present in the diagnostic biopsy Microinvasion is allowed
E.3	Uncontrolled intercurrent illness including (active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, pulmonary embolism in the past 6 months, or psychiatric illness/social situations that would limit

	compliance with study requirements).
E.4	Unable to comply with study requirements
E.5	Hormone therapies containing estrogen, progesterone, GnRH agonists and antagonists within 4 weeks from diagnostic biopsy.
E.6	Therapy with any CDK inhibitor in the past 3 months

Exclusion criteria specific to treatment Group A:

	Exclusion Criteria Specific for patients enrolled on Group A
E.7	History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib
E.8	Presence of a condition that would interfere with enteric absorption of palbociclib
E.9	Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to enrollment Breastfeeding must be discontinued prior to study entry (Group A only).
E.10	Patients on combination antiretroviral therapy, i.e. those who are HIV+ (potential for pharmacokinetic interactions or increased immunosuppression with palbociclib).
E.11	Patients receiving any medications or substances that are potent inhibitors or inducers of CYP3A isoenzymes within 7 days of enrollment or during participation on study (see **Section 4.4.5 Prohibited Therapy** for list of CYP3A inhibitors and inducers).
E.12	Patients with clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis, etc.

4.2 Registration Procedures

4.2.1 Study Site

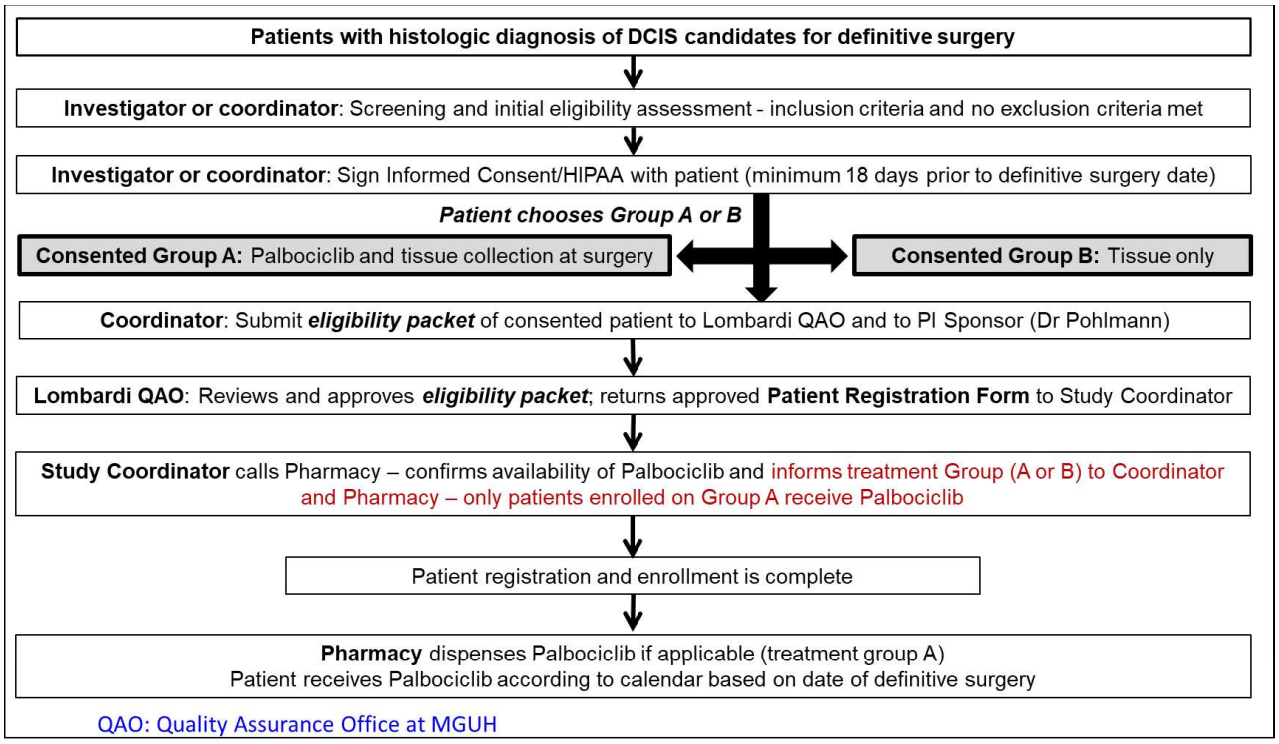
This study will be open at the MedStar Georgetown University Hospital/Lombardi Comprehensive Cancer Center (LCCC) and Medstar Washington Hospital Center.

4.2.2 Study Coordinators and Pharmacists

There will be a study coordinator overseeing the study. Lombardi Research Pharmacy will be responsible for dispensing Palbociclib according to Institutional SOPs for experimental treatments for oral use.

4.2.3 Patient Enrollment

Figure 4: Patient enrollment procedures:



Please refer to the procedures below for details on patient enrollment.

1. Study coordinator or treating physician screens patient for eligibility criteria.
    a. If patient does not meet eligibility criteria, stop and report screen failure and/or reason.
2. If patient meets initial eligibility screening, patient can sign informed consent and HIPAA authorization form. Consent can be obtained by study coordinator or treating physician.
3. Study coordinator or treating physician completes **Eligibility Checklist** in Appendix E.

a. Investigator signs and dates the eligibility checklist when all criteria are verified through review of source documents
b. **Eligibility Packet** is complete

4. Study coordinator or treating physician sends during business hours Monday - Friday between 8am and 4:30pm (EST) the full **Eligibility Packet** (outlined below) and completed **Lombardi Patient Registration Form** (Appendix F) to the following within 1 business day of investigator signing **Eligibility Checklist**:
    a. To the Lombardi Multicenter Project Manager (PM)
        i. Scanned/emailed toLCCC-Multicenter-IITs@georgetown.edu or
    b. And to Dr. Candace Mainor
        i. Scanned/emailed to [redacted] or
    c. In the event that there is a time constraint, please notify the research office to discuss possibility of expediting the process.
5. Lombardi PM verifies patient eligibility and returns approved Patient Registration Form with Subject Study ID information to the study coordinator.
    a. If patient's eligibility is not verified, stop.
6. If patient's eligibility is verified by Lombardi PM and a Subject Study ID is assigned, then the study coordinator does the following:
    a. Registers the patient on the study and in the database
    b. Calls the pharmacist at the study site to make sure Palbociclib is available for patients consenting treatment Group A
7. Study Coordinator scans to patient's EMR the completed Patient Registration Form (Appendix F). The original Patient Randomization Form must be stored in the study binder.
    a. Study coordinator emails patient study number and treatment Group (A or B) to treating physician, to the study pharmacist, and to PI-Sponsor (Dr. Candace Mainor).
8. Patient registration and enrollment is complete.
9. Patient receives first dose of Palbociclib according to calendar made by study coordinator observing the date of definitive surgery date (Appendix C).

The full **Eligibility Packet** must contain the following:

1) Signed and dated Eligibility Checklist (Appendix E); filled out completely and signed by investigator.
2) Signed and dated Lombardi Patient Registration Form (Appendix F). Typically, this form is signed by study coordinator. Exceptionally, in the absence of the study coordinator, this form can be signed by the investigator.
3) Signed and dated informed consent form
4) Signed and dated HIPAA form
5) All source documents required for verification of eligibility:
    a) Pathology report stating diagnosis of DCIS
    b) Confirmation of retrieval of archival tissue from diagnosis of DCIS

c) Pathology report stating Rb status positive
d) Tentative date for definitive surgery (Lumpectomy, Mastectomy, etc)
e) Clinic notes containing information on ECOG PS, previous and current treatments, co-morbidities, and information pertaining to eligibility for the trial
f) Current negative beta HCG test report (blood or urine) for women of childbearing potential – *Group A only*
g) Current Complete Blood Count with differential and Platelets – *Group A only*
h) Current Bilirubin levels and normal range at local laboratory – *Group A only*
i) Current Creatinine levels and normal range at local laboratory – *Group A only*
j) Current AST levels and normal range at local laboratory – *Group A only*
k) Current ALT levels and normal range at local laboratory – *Group A only*

The **informed consent form** should be uploaded to the patient's electronic medical record system, in addition to keeping the physical document signed by the patient and treating physician in the study binders, as per standard operating practice.

All participants must be registered and enrolled through the Oncology Research office at MedStar Georgetown University Hospital.

4.3 Study Treatment

Palbociclib will be provided by Pfizer. Patients enrolled on Group A will receive Palbociclib.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Formulation of Palbociclib

Palbociclib capsules for oral administration contain 125 mg, 100 mg, or 75 mg of palbociclib, a kinase inhibitor. The molecular formula for palbociclib is C H N O . The molecular weight is 447.54 daltons. The chemical name is 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(piperazin-1-yl) pyridin-2-yl]amino]-pyrido[2,3-d]pyrimidin-7(8H)-one. In this study, 100 mg capsules will be used. Those are opaque hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink "Pfizer" on the cap, "PBC 100" on the body.

4.3.1.2 Labeling of Palbociclib

Palbociclib Drug Substance and Drug Product are manufactured, labelled and packed according to current Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines for use in the clinical studies. Each lot of palbociclib for clinical studies is subjected to a series of quality control tests to confirm its identity, purity, potency, and quality.

4.3.1.3 Acquisition and Storage of Palbociclib

Palbociclib is an FDA approved drug, dispensed in bottles of 21 capsules of palbociclib 100mg (NDC 0069-0188-21). Palbociclib will be provided without charge to the patients or MedStar Georgetown University Hospital by Pfizer and given to the patients on Group A treatment arm. Pfizer will ship Palbociclib to study center, where it will be stored until dispensed. Appendix H shows the *Drug Supply Request Form* to be used by the pharmacist to request medication from Pfizer. Shipment of Palbociclib from Pfizer to the study site will be coordinated by a dedicated pharmacist. Palbociclib will be stored in the pharmacy until needed, as per standard operating procedures.

Palbociclib will be stored at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C to 30 °C (59 °F to 86 °F). Further storage and stability conditions are stated in the palbociclib IB.

Investigator and site staff are requested to check storage 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.

Deviations from the storage requirements, including any actions taken, must be documented and reported to the respective study Sponsor PI. Once a deviation is identified, palbociclib must be quarantined and not used until receipt of 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. Medication which has been returned by the patients should be stored separately from medication that needs to be dispensed.

4.3.1.4 Dispensation of Palbociclib

The dedicated pharmacist at each site will also be responsible for dispensing the drug to the treatment group patients, as per standard operating practices. Investigator will fill out the *Investigational Drug Order Form* (Appendix I) ordering Palbociclib for a patient. The coordinator will present the filled order form to the Pharmacist so that Palbociclib can be dispensed.

Study pharmacist will dispense 12 capsules for each participant enrolled to Cohort A (treatment cohort).

The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit and should further be instructed to keep their medication in the bottles provided and not transfer it to any other container. No other medicines should be added to palbociclib bottle.

Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

To ensure adequate records and patient compliance monitoring, palbociclib capsules will be accounted for by the site as instructed by the respective study Sponsor and following MGUH standard operational procedures. Hence, the study site pharmacy will maintain a careful record of the inventory and disposition of the agent. Accurate records of all investigational product received at, dispensed to, returned from, returned to, and disposed of by the study site should be recorded. Patients will be instructed to return previously dispensed bottles (including unused drug and/or empty bottles) as well as their completed Palbociclib Diary to the clinic at the pre-operative visit for accountability purposes

(Appendix J). Unused returned medication MUST NOT be re-dispensed to patients. The number of remaining capsules/tablets will be documented and recorded within the eCRF.

4.3.1.5 Palbociclib destruction or return

Sites will have to destroy or return unused Palbociclib. The site's principal investigator must ensure that any materials are destroyed or returned in compliance with applicable environmental local regulations, institutional policy, and any special instructions provided by Pfizer, Inc. Verification of drug accountability has to be completed before any IP is destroyed at site. Destruction or return of investigational product must be adequately documented.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Group A

Patients enrolled to **Group A** will receive a 12-day course of Palbociclib before surgery. They will receive Palbociclib 100mg PO daily x 12 days. When definitive surgery date is defined and Operation Room scheduled, day 1 of palbociclib will be determined and Palbociclib dispensed. Administration is performed on an outpatient, self-administration basis. Appendix C has a model calendar that can be used when planning events based on defined date of surgery.

- Treatment is continuous daily for 12 days, followed by 3 days off [+/- 1 day], followed by definitive DCIS surgery.
- Patients will be encouraged to take their dose of Palbociclib at approximately the same time each day.
- Palbociclib should be taken with food.
- If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.
- Palbociclib capsules should be swallowed whole (do not chew, crush or open them prior to swallowing).
- Capsules should not be ingested if they are broken, cracked, or otherwise not intact.
- Patients who inadvertently take 1 extra dose during a day must skip the next day's dose.
- If patient takes more than two doses of palbociclib in a day, the patient should bring this to the attention of his or her treating physician.
- Patients should be instructed to record daily administration of the study drug in the Palbociclib Diary (Appendix J**).**

4.3.2.2 Group B

These patients will receive no pre-operative treatment. Core biopsies from diagnosis and material from definitive surgery will be collected for translational studies and tissue banking. They will also provide blood samples at screening and prior to definitive surgery. Please refer to item **3.1.1 Overview of Study Design**, *timing of surgery*, for additional details on definitive surgery timing after enrollment for patients on Group B (no palbociclib).

4.3.2.3 Assessment of Compliance with Palbociclib

Study coordinator will meet with patient before surgery and after end of palbociclib treatment and collect empty bottles. At that point the coordinator will document compliance to treatment per protocol.

4.3.2.4 Other Required Medication

No other treatment will be required per protocol.

4.4 Concomitant Therapy

All prior treatment or medication administered during the 30 days prior to enrollment and any concomitant therapy administered to the patient throughout the study until date of surgery must be recorded on the respective page of the eCRF. The generic or trade name of the drug must be specified along with the dose, the duration of treatment, relation to AE and indication for use.

4.4.1 Surgery

Definitive surgery for DCIS treatment is permitted and should occur during participation on the trial.
If any other major surgery is urgently required, the patient will come off study and palbociclib discontinued.

4.4.2 Radiotherapy

Radiation therapy is not allowed before recovery from definitive surgery, or during participation on the trial. If radiation therapy is urgently required, the patient will come off study and palbociclib discontinued.

4.4.3 Hormone Therapy

Hormone therapy is not allowed during the trial. Patients receiving hormone therapy for previous diagnosis of DCIS or invasive cancer should discontinue this therapy at least 4 weeks prior to undergoing pre-treatment biopsy.

Hormone replacement therapies are allowed except for estrogen, progesterone, GnRH agonists and antagonists. Examples of allowed hormone therapies are insulin are levothyroxine.

4.4.4 Permitted Therapy

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 (**Section 4.4.5**).

4.4.5 Prohibited Therapy

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A. Use of the following concomitant therapies will not be permitted during the study:

- Strong CYP3A inhibitors

Coadministration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%. Examples of strong CYP3A inhibitors are clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole. Grapefruit or grapefruit juice should also be avoided during Palbociclib treatment.

- Strong CYP3A inducers

Coadministration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of Palbociclib in healthy subjects by 85%. Examples of strong CYP3A inducers are phenytoin, rifampin, carbamazepine, enzalutamide, and St John's Wort.

- Drugs That May Have Their Plasma Concentrations Altered by Palbociclib

Co-administration of midazolam with multiple doses of Palbociclib increased the midazolam plasma exposure by 61%, in healthy subjects, compared with administration of midazolam alone. The following sensitive CYP3A substrates with a narrow therapeutic index will not be allowed during participation on the study: alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus.

- Gastric pH Elevating Medications

In a drug interaction trial in healthy subjects, co-administration of a single 125 mg dose of Palbociclib with multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions had limited impact on AUC (13% decrease), when compared to a single dose of Palbociclib administered alone. Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid-reducing agents on palbociclib exposure under fed conditions is expected to be minimal. Under fed conditions there is no clinically relevant effect of PPIs, H2- receptor antagonists, or local antacids on palbociclib exposure.

4.5 Study Assessments

The study consists of 6 different phases:

1)	Pre-Screening Phase	(candidates for study either on Group A or Group B)	
2)	Screening Phase	(Group A and Group B)	*Study Days -28 to 0*
3)	Treatment Phase	(Group A only)*	*Study Days 1 to 12*
4)	Pre-Surgery Phase	(Group A only)*	*Study Days 12 to 14*
5)	Surgery	(Group A and Group B)*	*Study Days 14 to 16*
6)	Follow-Up Phase - EOV	(Group A and Group B)	*Study Days 25 to 40*
	Follow-Up Phase - LTF	(Group A and Group B)	*EMR review 1yr and 5yr*

* Please refer to item **3.1.1 Overview of Study Design**, *timing of surgery*, for additional details on definitive surgery timing after enrollment for patients on Group B

See **Appendix A Study Procedures** and **Appendix B Study Schema** for details as to how these phases correspond with the Schedule of Assessments calendar, Pre-Screening Phase, Screening Phase, Treatment Phase, Pre-Surgery Phase, Surgery and Follow-Up Phases End of Study Visit (EOV) and Long Term Follow Up (LTF).

4.5.1 Pre-Screening phase

Pre-Screening Phase is when the patient receives the diagnosis of DCIS based on pathology from a diagnostic procedure and is felt to be a candidate for the study. During this phase imaging studies are reviewed and case discussed among providers/investigators. On occasional circumstances DCIS may be suspected based on imaging, and yet to be confirmed by pathology diagnosis. In this case a biopsy should take place establishing the diagnosis of DCIS prior to confirming patient eligibility for the study.

4.5.2 Screening phase

The Screening Phase is the time between the date a patient provides written informed consent, and the time the patient completes enrollment procedures/has enrollment verified by the Lombardi Project Manager (PM). Data collection and procedures during this time period include patient demographics, eligibility requirements, concomitant medications, medical history, physical examination/vital signs, ECOG performance status assessment, baseline symptoms/adverse events, severe adverse events, laboratory measurements, pregnancy testing (if applicable), biospecimens (blood and tissue sample #1), and Rb testing. During the Screening Phase, only AEs deemed to be serious (SAEs) and related to protocol mandated and not routinely performed procedures have to be reported.

4.5.2.1 Pathologic diagnosis of DCIS - Biopsy

This procedure must be completed before registration by LCCC PM to trial. Typically, patient will be offered the trial after pathologic diagnosis of DCIS. However, the trial may be offered to patients prior to diagnostic biopsy, in case of highly suggestive radiological findings for DCIS. In this case, patients will need to complete diagnostic biopsy for eligibility. Fine needle aspiration is not acceptable. Patient can

undergo core biopsy, stereotactic biopsy or incisional biopsy of breast lesion, as long as the lesion is not completely resected during the procedure.

4.5.2.2 Rb Screening for Eligibility and Central Assessment of Hormone Receptor Status

All patients enrolled on this study will have baseline DCIS samples (Tissue sample #1) tested for Rb status at a CLIA-certified lab (for instance, MGUH Pathology Department) prior to registration. Rb staining will be done by immunohistochemistry and considered positive when 1+ or above (in a scale of 0, 1+, 2+ or 3+). Rb testing negative at screening is criterion for screen failure.

4.5.2.3 Medical History and Demographic Data

Demographic data will include age, sex, and self-reported race/ethnicity.

Medical history includes clinically significant diseases that are currently active or that were active, including major surgeries, within the previous 5 years, any cancer history (including prior cancer therapies and procedures) and reproductive status.

Patients may be considered postmenopausal in case that one of the following criteria applies:

- ✓ prior bilateral oophorectomy, OR
- ✓ Age ≥ 60 years, OR
- ✓ Age < 60 years with intact uterus and amenorrhoeic for ≥ 12 consecutive months* prior to chemotherapy and/or endocrine therapy exposure, OR
- ✓ Age < 60 years hysterectomized and FSH and plasma estradiol levels in the post-menopausal range according to local policies prior to chemotherapy and/or endocrine therapy exposure

If none of the above mentioned criteria fully applies, the patient may be judged premenopausal according to local policies. In the absence of procedure that prevents fertility (such as tubal ligation, hysterectomy, vasectomy) premenopausal patients must be tested negative for pregnancy prior to enrollment on Group A (Palbociclib treatment).

4.5.2.4 Physical Examinations and Vital Signs

At screening, a physical examination including a palpation of breast/chest wall, axillae, supra- and infraclavicular region, height, weight, blood pressure and pulse rate is required. Symptom-directed physical examinations, blood pressure, weight and pulse rate will be performed. All physical examinations and vital signs assessments should be performed by a physician or registered nurse or other qualified health care provider according to local regulations.

4.5.2.5 Radiology

All available radiology studies will be reviewed before treatment start. Questions may be discussed directly with radiologist, as well as at the weekly Lombardi Multidisciplinary Breast Cancer Meeting.

4.5.2.6 Laboratory Assessments

It is ideal that laboratory assessments be performed at the research center, since blood will also be collected for biorepository. During the Screening Phase, all laboratory assessments must be performed within 28 days of treatment start in Group A. In Group B, screening blood samples should be drawn at least 5 days prior to surgery date.

- Hematology:

Hemoglobin, white blood cell (WBC) count, absolute neutrophils and platelet count.

- Blood chemistry with liver function tests:

AST/ALT, alkaline phosphatase, sodium, potassium, CO2, chloride, total calcium, total bilirubin, serum creatinine, BUN, total protein and albumin.

- Serum/urine pregnancy test, if required

4.5.2.7 Mandatory Blood Samples for Biomarker Analysis

During screening phase blood samples will also be collected for storage at the Lombardi Biorepository. These are research samples.

Group A: In Group A there will be 3 time points for research blood collection.

1. The first research blood samples will be collected after consenting and prior to palbociclib treatment.
2. The second research blood sample will be collected after end of palbociclib and prior to surgery, typically on the date of surgery.
3. The third research blood sample will be collected after surgery (End of treatment visit).

Group B: In Group B there will be 2 time points for research blood collection.

1. The pre-operative research blood sample can be collected any time after consenting and prior to surgery in Group B.
2. The second research blood sample will be collected after surgery (End of treatment visit).

Appendix M contains the **Research Blood Sample Form,** to be filled on the day of sample collection and handling until its storage. Samples from this project will be stored at the Riegel Lab.

4.5.3 Treatment phase

During this phase, patients enrolled to treatment Group A will receive IP treatment (palbociclib). Treatment Phase for patients on Group A can start as soon as patient successfully completes screening and has the definitive date for surgery determined by the surgeon. Palbociclib starting date will be

defined by date of definitive surgery. The time period for this phase will be 14 to 16 days. This period starts on the date of dose #1 of Palbociclib. Palbociclib treatment is to be given for 12 days.

Patients enrolled to Group B will receive no treatment prior to surgery.

4.5.4 Pre-Surgery phase

For patients enrolled to **Group A**, on Day 13 +/-1 there will be a pre-operative clinic visit, when tolerance to therapy will be assessed, including physical examination/vital signs, ECOG performance status assessment, adverse events, serious adverse events, IP accountability, concomitant medications, measurements of treatment adherence. Laboratory tests will include CBC, CMP and an additional blood sample for research (please refer to item **4.5.2.7 Mandatory Blood Samples for Biomarker Analysis**). After this visit, patients will proceed to scheduled definitive surgery for DCIS. Treatment phase ends on the day of surgery (Day 15 +/-1).

For patients enrolled to **Group B** the pre-surgery experimental phase will only involve Laboratory tests including CBC, CMP and an additional blood sample for research (please refer to item **4.5.2.7 Mandatory Blood Samples for Biomarker Analysis**).

4.5.5 Surgery

On the scheduled day for surgery patient will follow surgery team's recommendations for hospital registration, OR procedures and subsequent discharge home. Surgery will occur on study day 15 +/-1. Research tumor sample will be collected under the supervision of certified pathologist (Tumor Sample #2). The research tumor sample will be transported to Riegel Lab where it will be processed and stored for testing. The surgery must happen at the study participating center.

4.5.6 Follow up phases – End of Study Visit and Long Term Follow Up

Follow-Up Phase starts on post operative day #1. The End of Study Visit (EOV) occurs on treatment day 32 +/- 8, which represents a time point situated approximately at 2 to 3 weeks after surgery. On that date, there will be a clinic visit with physical examination/vital signs, ECOG performance status assessment, adverse events, serious adverse events, current medications, and final pathology report. Additional treatments may be required after definitive surgery. Patient will discuss any additional treatments with the primary or treating medical oncologist. Laboratory tests will include CBC, CMP and an additional blood sample for research. A Long Term Follow up (LTF) assessment may be done at year 1 (+/- 30 days) and at year 5 (+/- 60 days) from treatment. The LTF assessment may comprise of Electronic Medical Record Review for clinical data and survival status as well as of a telephone call.

4.6 Patient and Study Discontinuation

Patients who are non-compliant or discontinue Study Treatment will be substituted. Withdrawal of consent for all study participation will end patient activity in the study, translational research and clinical follow up.

5. ASSESSMENT OF SAFETY

5.1 Safety Plan

Palbociclib is currently approved in the US for metastatic breast cancer and is currently in clinical development on other indications. The toxicity is considered predicable based on significant experience with palbociclib on phase I, II and III clinical trials, expanded access, and standard of care use.

5.1.1 Dose Delays and Modifications for Palbociclib

Palbociclib will be used at a lower dose of 100mg PO daily for 12 consecutive days. There will be no dose delays or dose reductions in this trial.

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 will be discontinued. Patients who discontinue study treatment (i.e. palbociclib for Group A) will continue to be followed according to post treatment follow up as defined in Schedule of Study Procedures (Appendix A).

5.1.2 Treatment discontinuation

Incidence, nature, and severity of adverse events triggering study treatment discontinuation 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), with respective attribution.

Any grade 3 or higher toxicity will trigger treatment discontinuation. 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.

5.1.3 Management of Specific Adverse Events

5.1.3.1 Neutropenia

Absolute neutrophil count (ANC) ≥ 1,500/mm^3 is required at baseline for study participation. Patients enrolled on treatment Group A will have a pre-surgery visit at day 13 +/-1 for clinical and laboratorial evaluation. Surgery will be scheduled to occur on day 15 +/- 1. If pre-operative counts reveal neutropenia, the definitive surgery will be postponed until recovery of neutrophil counts.

5.1.3.2 Thrombocytopenia

Platelets ≥ 120,000/mm^3 are required at baseline for study participation. Patients enrolled on treatment Group A will have a pre-surgery visit at day 13 +/-1 for clinical and laboratorial evaluation. Surgery will be scheduled to occur on day 15 +/- 1. If pre-operative counts reveal platelets lower than 80,000/mm^3, the definitive surgery will be postponed until recovery of platelet counts.

5.1.4 Pregnancy and Contraception Use

Pregnancy is contraindicated during Palbociclib therapy and for at least 3 weeks after the last dose. Based on findings from animal studies and its mechanism of action, Palbociclib can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryofetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on AUC. Patients will be advised regarding the potential risk of Palbociclib exposure to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

5.1.4.1 Adequate Non-Hormonal Contraception

Adequate contraception is defined as one highly effective form (i.e. abstinence, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusive cap with spermicidal foam / gel / film / cream / suppository).

5.1.4.2 Timing and Duration of Contraception

- Females

Palbociclib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential will be advised to use effective contraception during treatment with Palbociclib and for at least 3 weeks after the last dose.

- Males

Because of the potential for genotoxicity, male patients with female partners of reproductive potential will be advised to use effective contraception during treatment with Palbociclib and for 3 months after the last dose.

5.1.5 Lactation

There is no information regarding the presence of palbociclib in human milk, nor its effects on milk production or the breastfed infant. Because of the potential for serious adverse reactions in breastfed infants from Palbociclib, advise a lactating woman not to breastfeed during treatment with Palbociclib and for 3 weeks after the last dose.

5.1.6 Geriatric Use

Geriatric participation is allowed in this study. Of 84 patients who received Palbociclib in a study, 37 patients (44%) were ≥65 years of age and 8 patients (10%) were ≥75 years of age. Of 347 patients who

received Palbociclib in Study 2, 86 patients (25%) were ≥65 years of age. No overall differences in safety or effectiveness of Palbociclib were observed between these patients and younger patients.

5.2 Safety Parameters and Definitions

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

a. Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
b. Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
c. Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
d. Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms requires additional diagnostic testing or medical/surgical intervention, leads to a change in study treatment or concomitant treatment or discontinuation from study drug or is considered to be an AE by the Investigator.
e. Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment.

The investigator is responsible for ensuring that all adverse events (as defined above) are recorded on the respective Adverse Event eCRF page and additionally reported to the IRB in case the AE fulfills the criteria for expedited reporting.

For each adverse event recorded on an Adverse Event eCRF page, the investigator will make an assessment of seriousness, severity, and causality. The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by applicable regulations. Adverse events must be described and graded using the terminology and grading categories as defined by NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

For this protocol, serious adverse events (SAEs) are defined as follows:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to Palbociclib.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

This study will not have adverse events of special interest (AESI) for reporting.
There are no protocol-specified SAEs in this study.

5.2.4 Medication errors

Medication errors may result from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the Sponsor PI should be notified immediately (within 24hr from learning about the event).

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

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

5.3 Methods and Timing for Capturing and Assessing Safety Parameters

5.3.1 Adverse Event Reporting Period

Adverse event (Safety) reporting is mandatory from the date of informed consent form signature (i.e., screening phase) until the last visit of the treatment phase, 26 to 32 days after surgery. During the Screening Phase, only AEs deemed to be serious (SAEs) and related to protocol mandated and to non-routinely performed procedures have to be reported.

5.3.2 Eliciting Adverse Event Information

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

5.3.3 Assessment of Adverse Event Severity

The adverse event severity grading scale for the NCI CTCAE (v 4.0) will be used for assessing adverse event severity. 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. The grading system below will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

Legends:

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event,

[d] Grade 4 (only if immediately life threatening) and 5 events must be reported as serious adverse events

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the adverse event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the IP or Non-IP, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Adverse Event Attribution Categories:

Definitely	Direct association with study agent; clearly related
Probably	More likely explained by study agent
Possibly	Study agent and other cause explained equally well; maybe related
Probably Not	More likely explained by other cause; doubtfully related to the intervention
Unrelated	Clearly explained by other cause; clearly NOT related to the intervention

5.3.5 Procedures for Recording Adverse Events

5.3.5.1 Abnormal Laboratory Values

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing, or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or Sponsor
- Test causes delay of definitive surgery.

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

5.4 Immediate Reporting Requirements

5.4.1 Emergency Medical Contacts

Participating investigators must report each serious adverse event to the Sponsor within 24 business hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within business hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Candace Mainor, MD
Lombardi Comprehensive Cancer Center
3800 Reservoir Road NW, Podium C
Washington, DC 20007
Phone: [redacted]
[redacted]

The subject line of an email should clearly state that this is an urgent message regarding SAE on this study.

5.4.2 Serious Adverse Events Reporting Requirements

5.4.2.1 Reporting of Serious Adverse Events

When learning about and SEA (SAEs definition **section 5.2.2**), the Sponsor PI or their designee will notify:

1. The IRB and DSMC by a written safety report within one (1) business day of learning of the SAE;
2. Pfizer by facsimile within seven (7) calendar days of the first awareness of the event (immediately if the event is fatal or life-threatening), if:
    - Study subjects who are assigned to receive the Pfizer Product Palbociclib; or
    - Individuals otherwise exposed to the Pfizer Product as described below.

The Sponsor PI will provide additional details about the SAE to the IRB and DSMC, as well as Pfizer as it becomes available. Sponsor Principal Investigator should report SAEs as soon as they are determined to

meet the definition, even if complete information is not yet available. Within the following 1-2 business days of awareness, the participating investigator must provide follow-up information on the serious adverse event if a full description of events was not included with the initial reporting of the event to Sponsor PI. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation. Sub-investigators should submit this information to the Sponsor PI at [redacted].

Additional information that should be reported as SAEs include data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol.

All non-serious adverse events will be reported to the Sponsor on the adverse events CRFs.

As used in this Agreement, the term SAE will be understood to include exposure during pregnancy, exposure during lactation, and occupational exposure (refer to **section 5.4.2.2**).

5.4.2.2 Exposure during Pregnancy, Exposure during Lactation, Occupational Exposure

Even though there may not be an associated SAE, exposure to the Pfizer Product Palbociclib during pregnancy, during lactation, and occupational exposure are reportable. Abortions and congenital anomalies should also be reported.

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

5.4.2.4 SAE Reporting Period

The SAEs that are subject to this reporting provision are those that occur from after the first dose of Palbociclib through 28 calendar days after the last administration of the Pfizer Product. In addition, if Principal Investigator becomes aware of an SAE occurring any time after the administration of the last dose of the Palbociclib, Sponsor PI should report that SAE to Pfizer if a causal relationship between the Pfizer Product and the SAE is suspected.

5.4.2.5 Follow-Up Information

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

5.4.2.6 Regulatory Reporting

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

5.4.2.7 Pfizer-Provided Training

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

5.4.3 Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF.

The Sponsor PI will forward periodically listings of non-serious AEs originating from the study to Pfizer.

5.4.3.1 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/medwatch/getforms.html

5.4.4 Sponsor PI Reporting Requirements to Regulatory Authorities

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

5.4.4.1 Seven Calendar Day Telephone or Fax Report:

The Sponsor PI is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of palbociclib. An unexpected adverse event is one that is not already described in the palbociclib Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Pfizer within 7 calendar days of first learning of the event.

5.4.4.2 Fifteen Calendar Day Written Report

The Sponsor PI is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use

of Palbociclib. An unexpected adverse event is one that is not already described in the Palbociclib investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the Sponsor PI with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Pfizer and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:
Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Pfizer U.S. Clinical Trial Department at [redacted] (Cover sheet at Appendix K)

And to the Site IRB:
MedStar Georgetown University Hospital - Institutional Review Board
SW104 Medical Dental Building
3900 Reservoir Road, NW
Washington, DC. 20057
[redacted]

5.4.5 Reporting Forms:

Principal Investigator will report SAEs using a CIOMS I form (http://www.cioms.ch/index.php/cioms-form) or MedWatch 3500A (available at http://www.fda.gov/medwatch/getforms.html). The Reportable Event Fax Cover Sheet (Appendix K) provided by Pfizer must also be included with each SAE submitted.

The SAE Reporting Checklist is below:

- Use DD/MMM/YYYY format.
- Record all pertinent information on the SAE Report Form. **Do NOT** attach source documents (e.g., test results).
- Do NOT delay completing and submitting the SAE Report Form in order to obtain further information that could be submitted as a follow-up report.
- If a definitive assessment of causality is not possible at the time of the report, provide a preliminary assessment on the SAE page, and identify it as such in the **Event Narrative.**
- If the SAE is not deemed causally related to a study drug by the investigator, indicate in the **Event Narrative** the most likely cause (disease under study, other illness, etc.).
- If additional space is needed for any field, use additional copies of the same page.

- Use a new SAE Report Form when providing follow-up information or responding to queries. Do NOT cross out or add to the previous form.
- Obtain safety reporting contact information for your study from your Pfizer contact.
- Confirm not only that a faxed SAE Report Form was transmitted successfully, but also that it was transmitted to the correct fax number.

5.4.6 IND Annual Reports

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Pfizer.

5.4.7 Data Safety Monitoring Committee

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

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

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

All Severe Adverse Events (SAEs) are required to be reported to the IRB. In addition, all SAEs will be submitted to the DSMC at time of submission to IRB and to Pfizer. Based on SAEs, the IRB retains the authority to hold accrual for the study pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients. DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the Sponsor PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 Determination of Sample Size

There will be two participating centers in this study: MGUH and MWHC. This is a prospective pilot study designed to assess the feasibility and potential translational changes of preoperative treatment with palbociclib–of patients with Rb positive DCIS of the breast. The primary endpoints are feasibility and pathologic changes (histology, IHC and molecular analysis) comparing paired samples from before and after short course of systemic treatment (diagnostic core vs definitive surgery, in each patient). The secondary endpoint is descriptive toxicity.

The estimated sample size of 12 patients per study Group is decided based on typical sample size requirement for a pilot study[56] because parameters for expected pathologic changes caused by palbociclib in this disease are not available. *The total number of patients in this study will be 24.* The statistical analysis will be mostly descriptive due to the nature of the study and the small sample size. It will be performed after study completion. Baseline and follow-up data will be summarized using basic descriptive statistics such as means and standard deviations for the continuous variables and frequencies and percentages for categorical variables. For continuous outcome, the median and range will be reported. For binomial outcome, the proportion will be estimated along with its confidence interval estimated using exact method. Changes in the tumor histologic or molecular parameters from baseline to end of treatment will be tested using paired t-tests for continuous variables and McNemar's test for paired proportions. Repeated measures data will be analyzed using linear growth curve models that will allow us to identify and estimate individual-level growth tracks for the patients. Survival models (time to event) will be used as sample size permits to evaluate disease progression among all patients.

LCCC Biostat Unit will be responsible for designing the study and conducting data analysis which will be directed by Dr. Ming Tan.

7. DATA COLLECTION AND MANAGEMENT

7.1 Data Quality Assurance

During study conduct, the MedStar Georgetown University Hospital/Lombardi Comprehensive Cancer Center Quality Assurance Office (QAO) and/or Project Manager(s) (PM) will conduct periodic monitoring to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The LCCC/QAO or PM monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

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

7.2 Electronic Case Report Forms

As used in this protocol, the term CRF should be understood to refer to an electronic data record. A CRF is required and should be completed for each included patient.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. Laboratory results and concomitant medications will be collected on the CRFs. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

7.3 Source Data Documentation

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

7.4 Retention of Records

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

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

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

8. ETHICAL CONSIDERATIONS

8.1 Institutional Review Board or Ethics Committee

All oncology clinical research protocols must be submitted to the Clinical Research Committee (CRC) for scientific review before submission to and final approval by the IRB. The initial review includes an assessment of the specific plans for data and safety monitoring, which vary depending on the study type, phase, size, and sponsorship.

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB. All correspondence with the IRB/EC should be retained in the Investigator File. Copies of IRB approvals should be forwarded to Pfizer.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

8.2 Informed Consent

This study will be conducted in accordance with FDA regulations, the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable local, state, and federal laws. The informed consent/assent document(s) used during the informed consent process must be reviewed by the Sponsor, approved by the IRB before use, and available for inspection. The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited she cannot reasonably be consulted, as permitted by the IRB and consistent with local regulatory and legal requirements, then the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide her own consent, the source documents must record why the patient did not provide consent (e.g., decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study

subject and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

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

Patients will be informed that participation is voluntary and not necessary for receiving standard of care chemotherapy for their cancer and that they can choose to withdraw consent from the study at any time. This will also be documented in writing on the consent form.

The study will not include participants less than 18 years of age. For adult participants who lack decision-making capacity, the legally authorized representative will serve as the proxy. In the event a patient or their proxy does not read, write, or understand English, a trained medical interpreter must be present, either in person or via phone or video remote access, to translate.

8.3 Subject Compensation

Subjects will not be compensated in cash or in kind.

8.4 Confidentiality

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by laws. Personal information about the patients, including but not limited to name, date of birth, sex, race, ethnicity, previous treatment (including but not limited to pathology reports, imaging reports, laboratory reports, surgery, radiation oncology, medical oncology, etc.), office notes, physical exam, history, medications, adverse events, etc. will be collected on each study patient. This data is important for evaluating the primary and secondary endpoints of the study and will be protected from improper use and disclosure as per MedStar standard operating procedures. This plan will be implemented at the time of signing consent for each patient.

Protected Health Information (PHI) will be accessed in this study. PHI will be received via a CRF and also be recorded in a CRF. PHI information will be retained until all follow up publications and studies stemming from this study have been completed. This information will only be shared within the research team. Confidentiality will be maintained via standard MedStar standard operating procedures. All electronic transmission of PHI data will be in encrypted/secured form. No names of subjects will be included in the publication. No digital, video, audio, or photographic recordings of the subject will be made public.

When study data is compiled for transfer to any authorized parties, patient names, addresses and other identifiable data will be replaced by a numerical code consisting of a numbering system in order to de-identify study patients. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will

maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws.

All hardcopy and electronic data will be kept in accordance with the MedStar standard operating procedures. Upon completion of all publications related to this study, the data will be destroyed in accordance with institutional protocols. No members other than those on the research team will have access to the study data. Data will not be shared outside of the research team.

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

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

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

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

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

c. Other Protocol Deviations/Violations: All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

   • Is generally noted or recognized after it occurs
   • Has no substantive effect on the risks to research participants
   • Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
   • Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).

• Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

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

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

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

8.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required. The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

8.7 Financial Disclosure

Investigators will provide Pfizer and regulatory authorities with adequate and accurate financial information in accordance with local regulations and laws in order to allow Pfizer to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing updated information on financial interests during the course of the study as well as for 1 year after completion of the study.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by MHRI or LCCC. All investigators will follow the MHRI and LCCC conflict of interest policy.

8.8 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. Minor deviations should be summarized and reported to the IRB at the time of continuing review. Major deviations should be summarized and reported to the Regulatory Affairs Coordinator who will submit to the IRB as soon as possible, but not more than 10 calendar days after acquiring information reasonably suggesting that a reportable (major) deviation has occurred.

9. REQUIRED DOCUMENTATION

Before the study can be initiated at any site, the following documents must be filed at MGUH Regulatory (Study Binder):

- Original U.S. FDA Form 1572. The names of all investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations;
- Sponsor-PI's and sub-Investigator's medical licenses, CITI training, Current curriculum vitae
- Written documentation of IRB approval of protocol and informed consent document;
- A copy of approved protocol
- A copy of the IRB-approved informed consent document and IRB communications;
- CRC communication
- A signed Clinical Research Agreement
- Delegation of authority log
- Lab CAP/CLIA, Laboratory normals
- Any sponsor communication, including newsletters
- Monitoring visits letters – pre/post

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Appendix A: Study procedures

	Screening Phase		Treatment Phase		Pre-surgery	Surgery	Folow up Phase	
Procedure	Screening	Pre-treatment	Treatment start	Last day of treatment	Pre-surgery	Day of Surgery	End of Treatment visit	Long term follow up
Day	**(-)28 to (-)1**	**(-)28 to 0**	**1**	**12**	**13 +/-1**	**15 +/-1**	**32 (+/- 8 days)**	**1yr and 5yr**
Signed Informed Consent Form(s)	x							
Review of Eligibility Criteria	x	x						
Clinical Visit	x[9]	x[7]			x[7]		x	
Review of breast US, Mammograms and breast MRI if available	x							
Disease status	x	x[4]			x[4]		x	x [6]
CTCAE v. 4.03 review of baseline toxicities		x			x[4]		x	
Archival tumor tissue specimen or 15 unstained slides	x							
Rb testing archival tissue	x[1]							
Tissue for research at definitive surgery						x[5]		
CBC/diff/platelets	x[8]	x[4]			x[4]		x	
CMP	x[8]	x[4]			x[4]		x	
Coags (aPTT, INR)	x[8]							
Serum or unrine pregnancy test	x							
Blood sample for research - cells		x [2]			x [2,4]		x [2]	

	Screening Phase		Treatment Phase		Pre-surgery	Surgery	Folow up Phase	
Procedure	Screening	Pre-treatment	Treatment start	Last day of treatment	Pre-surgery	Day of Surgery	End of Treatment visit	Long term follow up
Day	**(-)28 to (-)1**	**(-)28 to 0**	**1**	**12**	**13 +/-1**	**15 +/-1**	**32 (+/- 8 days)**	**1yr and 5yr**
Schedule definitive surgery date		x						
Group A: Start palbociclib			x[3]					
Group B: no treatment								
Lumpectomy or mastectomy						x		
Pathologic exam of specimen						x		
EMR review							x	1yr and 5yr
Telephone contact							x	1yr and 5yr

1 Rb testing for all participants at screening. Rb negative configures screen failure.

2 Research blood sample for liquid biopsy and tissue banking (serum/plasma and PBMCs). In Group B, pre-operative sample can be drawn any time after consenting and prior to surgery. For details on these samples please refer to item **4.5.2.7 Mandatory Blood Samples for Biomarker Analysis**

3 Palbociclib 100mg PO daily for 12 days; provided by Pfizer and to be dispensed by MGUH/WHC research pharmacy.

4 Group A only.

5 Tissue sample #2: Under supervision of the certified pathologist, the sample required for pathologic diagnosis will be collected. Excess tissue will be used for research. Research tumor samples will be collected for H&E and IHC (formalin), CRC cultures (conditionally reprogrammed cell media), isolation of RNA and subsequent expression analysis, and for proteomic or metabolomic analysis (Snap Frozen). Non used tissue will be banked. Handling, processing, storage and testing DCIS sample at definitive surgery by pathologist and at Lombardi Research Lab (RIEGEL LAB)

6 Evaluation of clinical characteristics including disease status by EMR review and telephone contact

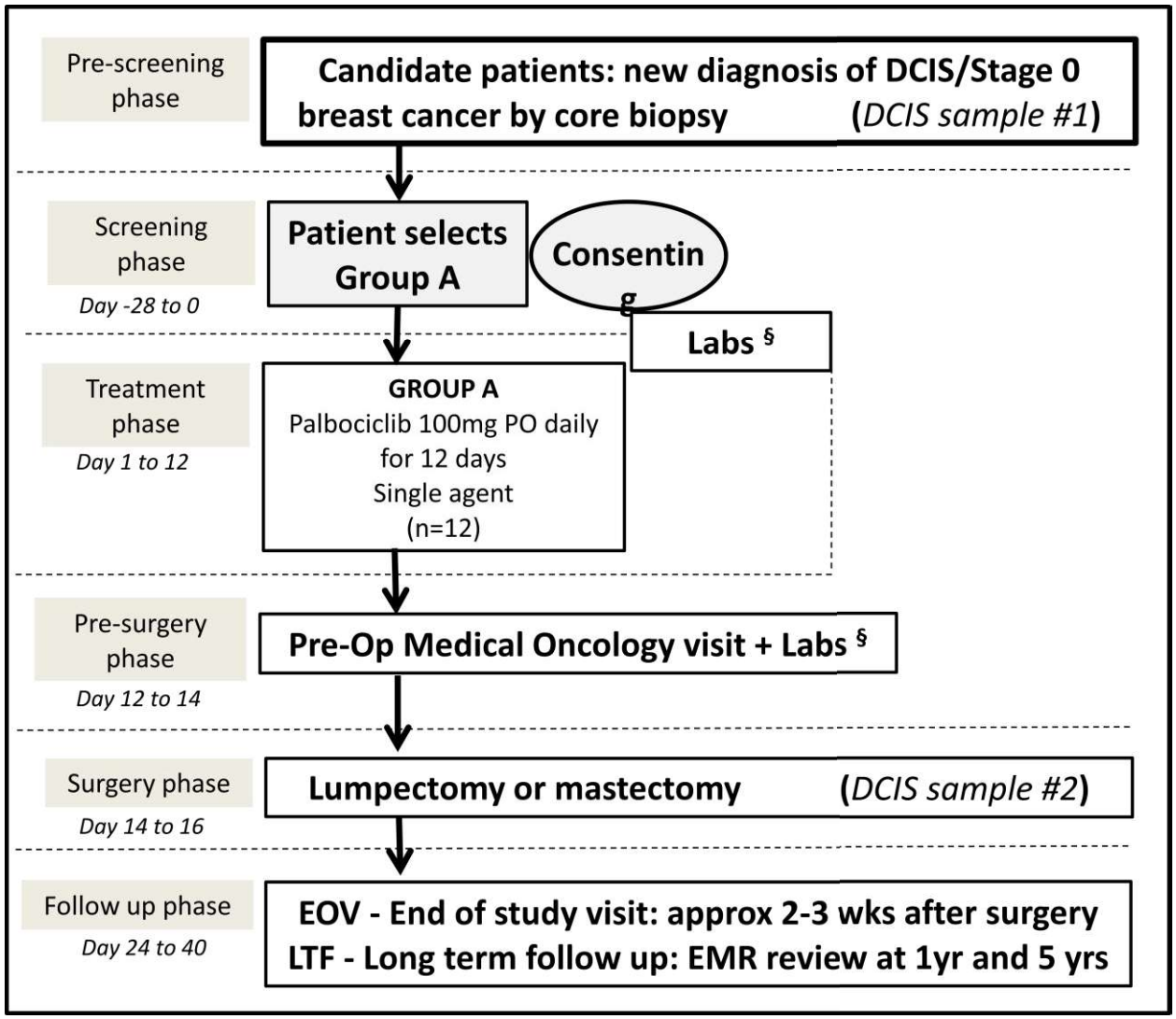
7 Additional visits will be required for patients enrolled on Group A. These include a visit with Medical Oncology team prior to initiation of palbociclib (pre-Treatment) and another visit after end of palbociclib, prior to surgery (pre-Surgery). These visits are not required for patients enrolled in Group B.

8 Tests must be completed at least 5 days prior to definitive surgery in Group B (untreated)

9 Clinical visit –(28) to (-)1 is the routine visit typically with the surgeon to discuss newly diagnosed DCIS and surgical plan, at which point the study may be offered to the patient (Group A and B).

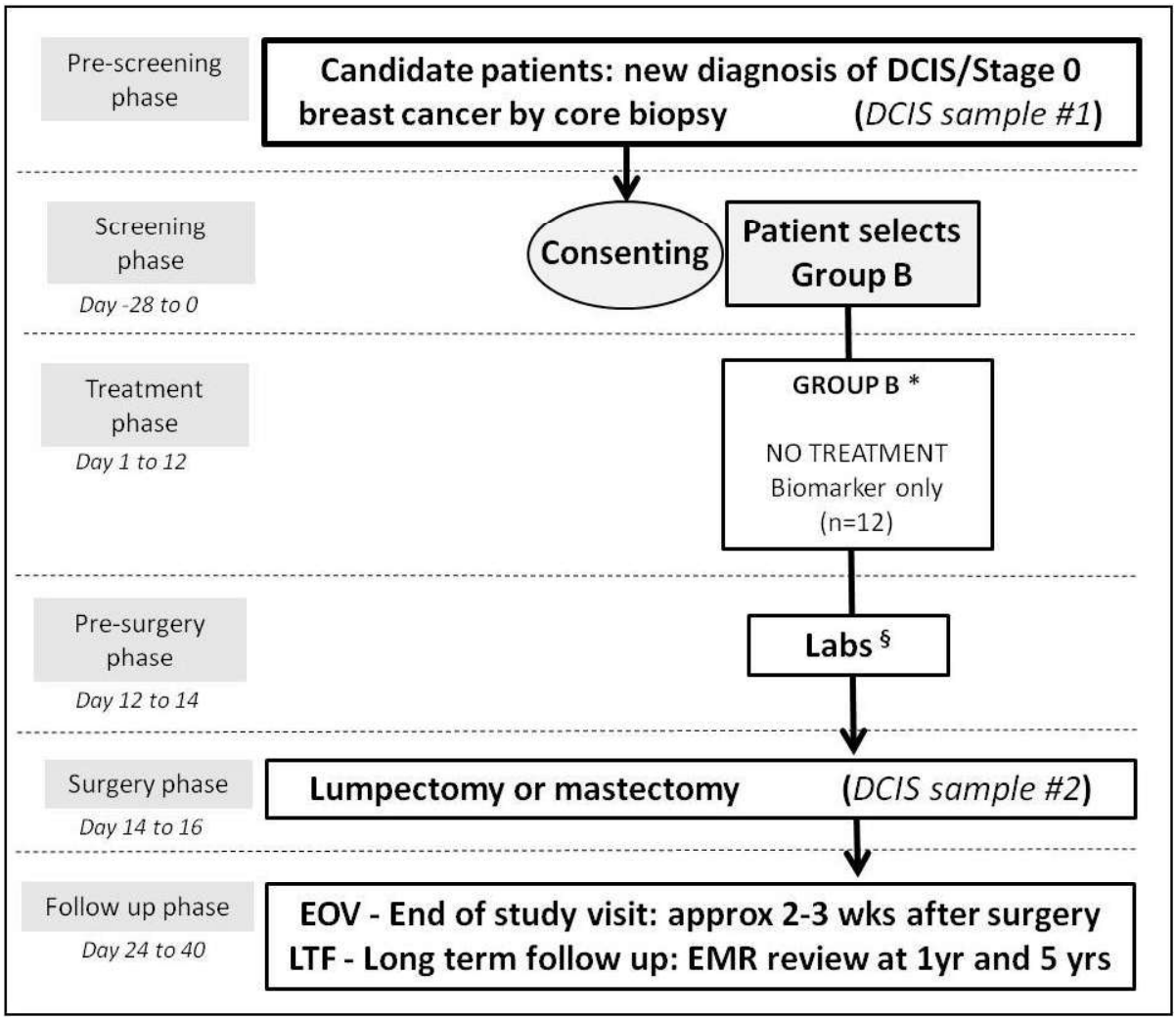
Appendix B: Study schema

Group A – Palbociclib treatment:



§ Please refer to item **4.5.2.7 Mandatory Blood Samples for Biomarker Analysis**

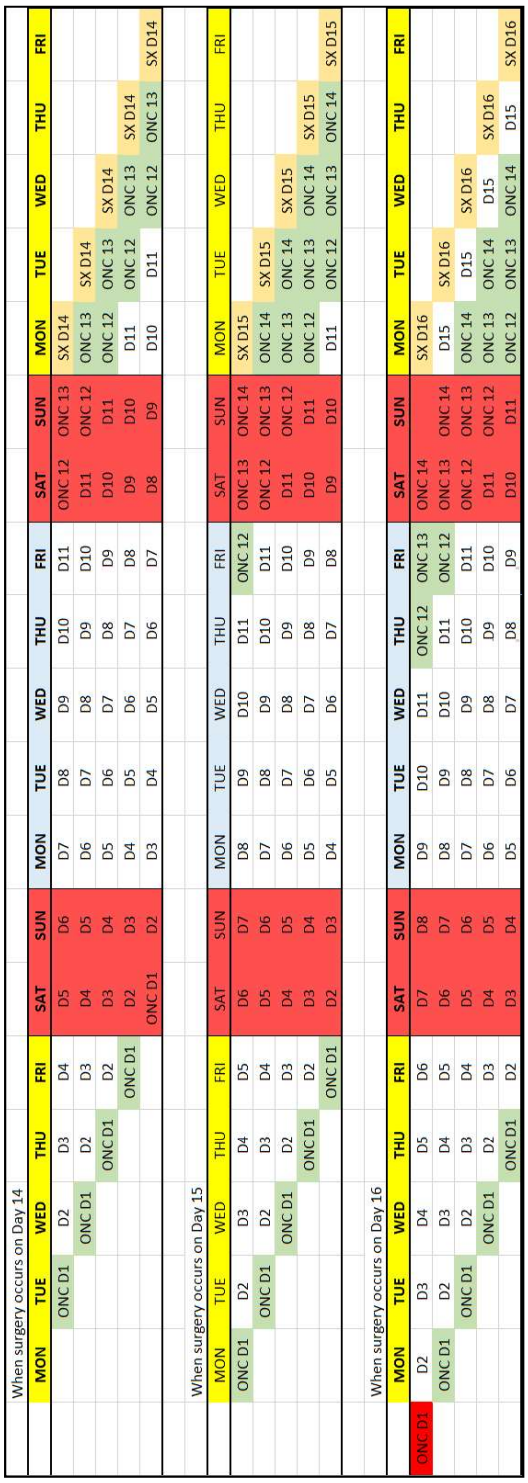
Group B – tissue only:



* Please refer to item **3.1.1 Overview of Study Design**, *timing of surgery*, for additional details on definitive surgery timing after enrollment for patients on Group B (no palbociclib).

§ Please refer to item **4.5.2.7 Mandatory Blood Samples for Biomarker Analysis**

Appendix C: Calendar for treatment planning based on surgery date for Group A patients



When surgery occurs on Day 14

MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI
	ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	SX D14				
		ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	SX D14			
			ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	SX D14		
				ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	SX D14	SX D14
					ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	

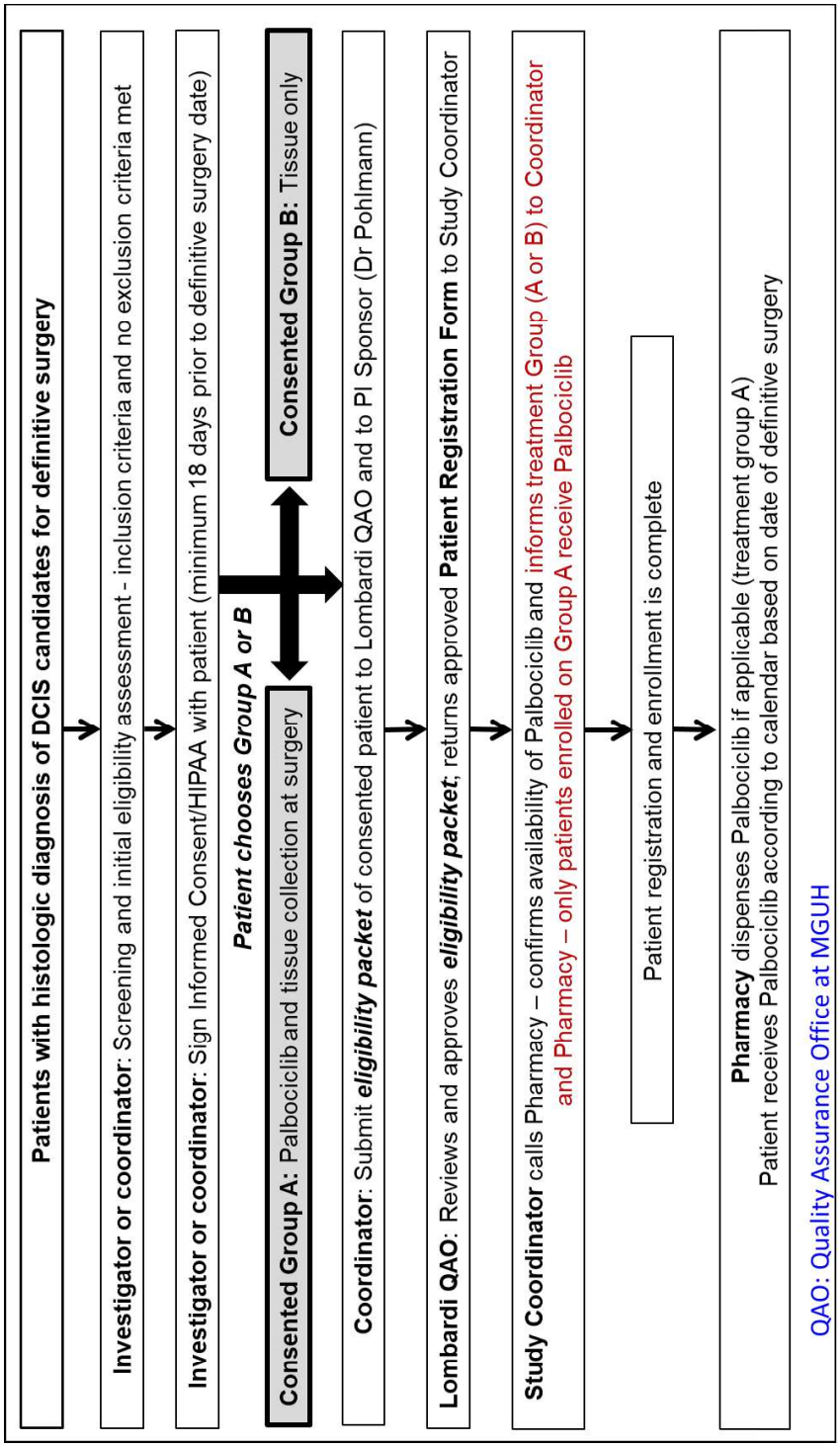
When surgery occurs on Day 15

MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI
ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14	SX D15				
	ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14	SX D15			
		ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14	SX D15		
			ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14	SX D15	SX D15
				ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14	SX D15

When surgery occurs on Day 16

MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI	SAT	SUN	MON	TUE	WED	THU	FRI
ONC D1	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14		SX D16				
ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14	D15	SX D16			
	ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14	D15	SX D16		
		ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14	D15	SX D16	SX D16
			ONC D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	ONC 12	ONC 13	ONC 14	D15	SX D16

Appendix D: Enrollment Process to Treatment Overview



Appendix E: Eligibility Checklist

Study Title: **Palbociclib in patients with DCIS of the breast that are candidates for surgery**

Patient Initials: _____ Study ID (IRB#): **2018-0075**

TO THE INVESTIGATOR, PLEASE CHECK BELOW IF YOU AGREE:

( ) Eligibility reviewed and confirmed by investigator, to be reviewed by LCCC PM

Enrolling MD (Print name): _____

Signature: _____ Date _____/_____/_____

Inclusion Criteria				
#	**YES**	**NO**	**N/A**	**For all patients (both Groups A and B)**
I.1				Signed informed consent obtained prior to any study specific assessments and procedures
I.2				Age ≥18 years
I.3				Premenopausal and postmenopausal women or men
I.4				Current pathologic diagnosis of DCIS of the breast of any receptor status; a) History of previous DCIS allowed provided that the patient is currently off systemic risk-reduction endocrine therapy; b) History of previous invasive breast cancer adequately treated and that is currently in remission and unrelated to current DCIS (based on primary tumor location) is allowed as long as patient is currently off systemic therapy for that invasive cancer for at least 4 weeks prior to pre-treatment biopsy (diagnostic biopsy); c) Patients with multifocal or multicentric lesions are allowed, as long as one lesion is histologically confirmed DCIS and overall clinical AJCC Stage I.
I.5				A formalin-fixed paraffin-embedded (FFPE) tumor tissue block from diagnostic biopsy must be transmitted to MedStar Georgetown University Hospital Pathology Department repository and confirmation of receipt must be available prior to enrollment.

Inclusion Criteria (continuation)				
#	YES	NO	N/A	For all patients (both Groups A and B)
I.6				Positive Rb by immunohistochemistry in the DCIS component of the lesion a) Must be performed at CLIA-approved setting (for instance, MGUH) b) Rb staining will be considered positive when 1+ or above (in a scale of 0, 1+, 2+ or 3+)
I.7				In the absence of histologic diagnosis of DCIS, patient may undergo fresh biopsy for eligibility, provided: a) This invasive procedure is not a Fine Needle Aspiration (FNA); AND b) This procedure is a core biopsy, stereotactic biopsy or incisional biopsy of the suspicious breast lesion; AND c) The primary lesion is not completely resected during the procedure.
I.8				The patient is candidate for and is willing to receive definitive surgical therapy for DCIS
I.9				ECOG performance status 0-1 (Appendix G: ECOG PS scale).
I.10				Willingness to provide a sample of tissue collected at definitive surgery for research.

Inclusion Criteria				
#	YES	NO	N/A	Specific for patients enrolled on Group A
I.11				Patients must be able and willing to swallow and retain oral medication
I.12				Absolute neutrophil count (ANC) ≥ 1,500/mm^3
I.13				Platelets ≥ 120,000/mm^3
I.14				Hemoglobin ≥ 10g/dL
I.15				Total serum bilirubin ≤ ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert's Syndrome.

I.16				Aspartate amino transferase (AST or SGOT) and alanine amino transferase (ALT or SGPT) ≤ 1.5 × institutional ULN
Inclusion Criteria (continuation)				
#	**YES**	**NO**	**N/A**	**Specific for patients enrolled on Group A**
I.17				Serum creatinine within normal institutional limits or creatinine clearance ≥ 50 mL/min/1.73 m^2 for patients with serum creatinine levels above institutional ULN.
I.18				Pregnancy must be ruled out: a) Serum or urine pregnancy test must be negative within 14 days of treatment start in women of childbearing potential. b) Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before enrollment, or who have undergone tubal ligation, bilateral oophorectomy, total hysterectomy
I.19				Willingness to undergo adequate contraception if childbearing potential a) Women of childbearing potential and male patients randomized into treatment Group A must use adequate contraception for the duration of protocol treatment and for 3 months after the last treatment with palbociclib if they are in Group A. b) Adequate contraception is defined as one highly effective form (i.e. abstinence, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusive cap with spermicidal foam / gel / film / cream / suppository).

Exclusion Criteria				
#	**YES**	**NO**	**N/A**	**For all patients (both Groups A and B)**
E.1				Concurrent therapy with other Investigational Products.
E.2				Invasive carcinoma present in the diagnostic biopsy • Microinvasion is allowed
E.3				Uncontrolled intercurrent illness including (active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, pulmonary embolism in the past 6 months, or psychiatric illness/social situations that would limit compliance with study requirements).

E.4				Unable to comply with study requirements
E.5				Hormone therapies containing estrogen, progesterone, GnRH agonists and antagonists within 4 weeks from diagnostic biopsy.
E.6				Therapy with any CDK inhibitor in the past 3 months

Exclusion Criteria				
#	YES	NO	N/A	Specific for patients enrolled on Group A
E.7				History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib
E.8				Presence of a condition that would interfere with enteric absorption of palbociclib
E.9				Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to enrollment . Breastfeeding must be discontinued prior to study entry (Group A only).
E.10				Patients on combination antiretroviral therapy, i.e. those who are HIV+ (potential for pharmacokinetic interactions or increased immunosuppression with palbociclib).
E.11				Patients receiving any medications or substances that are potent inhibitors or inducers of CYP3A isoenzymes within 7 days of enrollment or during participation on study (see **Section 4.4.5 Prohibited Therapy** for list of CYP3A inhibitors and inducers).
E.12				Patients with clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis, etc.

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

Appendix F: Lombardi Patient Registration Form

INSTRUCTIONS FOR STUDY COORDINATOR: This 2-page form and all supporting documentation should be completed by the research staff and scanned/emailed to [redacted] and Dr. Candace Mainor, [redacted]

Patient Initials: _____ Study ID (IRB#): **2018-0075**

Study Coordinator name: _____ Signature: _____

Date _____/_____/_____

1. Site PI: _____
2. Enrolling MD: _____
3. Date Informed Consent signed: _____/_____/_____
4. Date HIPAA authorization signed: _____/_____/_____
5. Study Group: ( ) Group A (pre-operative 12-day course of Palbociclib 100mg daily PO)
   ( ) Group B (No pre-operative treatment)
6. Proposed start date for Palbociclib (Day 1) ( ) Group A: _____/_____/_____
   ( ) Group B: *Non applicable*
7. Date of Pathological diagnosis of DCIS: _____/_____/_____
8. Please email **eligibility packet** to: (1) LCCC PM; and to (2) Sponsor-PI Dr. Mainor

☐ *Lombardi Patient Registration Form* (Appendix F) - this form filled out completely and signed by the Study Coordinator

☐ *Eligibility Checklist* (Appendix E) filled out completely and signed by the Investigator

☐ Signed and dated informed consent form

☐ Signed and dated HIPAA form

☐ Pathology Report stating DCIS diagnosis

☐ Pathology Report stating DCIS is Rb +

☐ Confirmation of retrieval of archival tissue from diagnosis of DCIS

☐ Tentative date for definitive surgery (Lumpectomy, Mastectomy, etc.)

☐ Physician's Note

☐ ECOG score

☐ Past Medical History

☐ Concomitant medication list

☐ Current negative beta HCG test report (blood or urine) for women of childbearing potential – **Group A only**

☐ Laboratory Results (CBC, CMP) – **Group A only**

☐ Other _____

ON-STUDY CARD – Study 2018-0075

MRN: _____

DOB: _____/_____/_____

Treating Physician _____ RN_____

Zip Code: _____

Race ( ) African American
( ) Asian
( ) Caucasian
( ) Hispanic
( ) Native American
( ) Pacific Islander
( ) Other
( ) Unknown

Gender: ( ) Male ( ) Female ( ) Unknown

Ethnicity: ( ) Hispanic or Latino
( ) Not Hispanic or Latino
( ) Unknown

Consent Approval Date: _____/_____/_____

Screen Failure ( ) Yes ( ) No

On Study Date _____/_____/_____

Protocol Waiver: ( ) Yes ( ) No

Reason _____

First Scheduled Treatment Date (Group A only): _____/_____/_____

FOR LCCC-PM USE ONLY:

Eligibility verified: ( ) Yes ( ) No

Subject Study ID: _____

PM name: _____ Signature: _____

Date _____/_____/_____

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

Appendix G: Eastern Cooperative Oncology Group (ECOG) Performance Status

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

As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.[57]

Appendix H: Drug Supply Request Form

Appendix I: Investigational Drug Order Form (Palbociclib)

Appendix J: Palbociclib Diary (Group A)

Patient #: _____ Date (mm-dd-yyyy) _____ / _____ / _____

Treatment start date (mm-dd-yyyy) _____ / _____ / _____

Treatment end date (mm-dd-yyyy) _____ / _____ / _____

Study **2018-0075**

Day	Date (MM-DD-YYYY)	Time (write the time you took palbociclib in hh:mm format)	Comments
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			

- ✓ "Day 1" is the first day of the 12-day pre-operative treatment course. The treatment may start on any calendar date; thus a Treatment Day does not usually match the calendar date.
- ✓ Take one capsule of Palbociclib 100 mg by mouth with water daily at approximately the same time each day. Palbociclib should be taken with food.

- ✓ Take Palbociclib capsules whole – do not chew, crush or open them prior to swallowing.
- ✓ Palbociclib capsules should not be ingested if they are broken, cracked, or otherwise not intact.
- ✓ If you miss a dose or vomit after dosing, do not retake this medication. Document it in this medication diary and report it to your health care provider at your next visit.
- ✓ Write the date and time when you took your medication at home
- ✓ Keep Palbociclib capsules out of reach of children.
- ✓ The Palbociclib capsules need to be stored in the original package. Please see product label for appropriate storage conditions.
- ✓ You will receive a Palbociclib Diary and Palbociclib supply at the first day of the treatment.
- ✓ If, for any reason, you run out of Palbociclib capsules, or anticipate running out before your next clinic appointment, please contact the research nurse at [redacted] or [redacted] IMMEDIATELY.
- ✓ While you are taking Palbociclib capsules, always bring your medication bottle even if empty and/or unused capsules to the clinic to your next visit.

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

Appendix K: Reportable event fax cover sheet

REPORTABLE EVENT FAX COVER SHEET

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

Include with this form the completed Pfizer 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 Pfizer 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 Pfizer 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:	*Pfizer U.S. Clinical Trial Department*	
FAX:	[redacted]	
FROM:		DATE:
TELEPHONE:		FAX:
NUMBER OF PAGES (INCLUDING COVER SHEET):		
PRODUCT	Ibrance® (palbociclib)	
PFIZER REFERENCE NUMBER	WI223281	EXTERNAL REFERENCE NUMBER
STUDY TITLE	*FULL Preoperative palbociclib in women with DCIS of the breast that are candidates for surgery*	
PATIENT NUMBER		
INVESTIGATOR	Paula Pohlmann, MD, MSc, PhD	

Confidentiality Notice: The documents accompanying this telecopy transmission contain information belonging to Pfizer, which is intended only for the use of the addressee. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution, or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for the return of the original documents to us. Thank you.

Appendix L: Pathology Form

Preoperative palbociclib in patients with DCIS of the breast that are candidates for surgery: WI223281

Subject Registration Number on Study: _____

Study ID (IRB#): **2018-0075**

Date _____/_____/_____

Name of Pathologist: _____ Signature: _____

Person filling the form if different than pathologist:

_____ Signature: _____

Definitive surgery: ☐ Mastectomy ☐ Lumpectomy

Check list:

- ☐ Sample collected for routine pathology exam

Research sample:

- ☐ No sample available for Research
- ☐ Sample collected for research

Research procedures:

- ☐ Sample in Research Media for Riegel's lab
- ☐ Sample in CRC media
- ☐ Sample delivered at Riegel's lab on date: ____/_____/_____

  Time: ____:_____AM/PM

  By _____ (Name)

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

Appendix M: Research Blood Sample Form

Preoperative palbociclib in patients with DCIS of the breast that are candidates for surgery: WI223281

Subject Registration Number on Study: _____

Study ID (IRB#): **2018-0075**

Date _____/_____/_____

Name of Study Coordinator: _____ Signature: _____

What is this the time point of this research blood sample?

Group A (palbociclib)

- ☐ Blood sample #1 (pre-palbo)
  - Plasma
  - PBMC
- ☐ Blood sample #2 (pos-palbo and pre-surgery)
  - Plasma
  - PBMC
- ☐ Blood sample #3 (post-surgery)
  - Plasma
  - PBMC

Group B (observation)

- ☐ Blood sample #1 (pre-palbo)
  - Plasma
  - PBMC
- ☐ Blood sample #2 (post-surgery)
  - Plasma
  - PBMC

☐ Sample delivered at Riegel's lab on date: ____/_____/_____

Time: ____:_____AM/PM

By _____ (Name)

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD