Palbociclib in Combination with Fulvestrant or Tamoxifen as Treatment for Hormone Receptor Positive Metastatic Breast Cancer with Prior Chemotherapy for Advanced Disease: A Phase II study with Pharmacodynamics Markers (TBCRC035)

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Protocol No.: CC#147522 **Version Date:** 03/03/16

1. I agree to follow this protocol version as approved by applicable ethical review board(s) such as a Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

Site Principal Investigator

_____
Printed Name

_____ _____
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Title

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Name of Site

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Site Principal Investigator: Please SIGN and DATE this signature page. PRINT your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to HCRN and keep a copy for your files.

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Participating Site(s)

Baylor College of Medicine	Georgetown University	Dana-Farber Cancer Institute
University of Chicago	Indiana University	University of Michigan
University of Pittsburgh	Vanderbilt University	Johns Hopkins University
The University of Alabama at Birmingham		

Central Trial Management by:

Hoosier Cancer Research Network (HCRN)

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[redacted]

Abstract

Title	Palbociclib in combination with fulvestrant or tamoxifen as treatment for hormone receptor positive (HR+) metastatic breast cancer with prior chemotherapy for advanced disease: a phase II study with pharmacodynamic markers.
Patient population	Post or pre-menopausal women over 18 years of age, with histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent and who have received at least one and not more than 3 prior lines of chemotherapy for advanced disease.
Hypotheses	Inhibition of cyclin dependent kinases 4 and 6 (CDK 4/6) with fulvestrant or tamoxifen in patients with advanced breast cancer and prior exposure to chemotherapy will be well tolerated, without an increase in grade 3/4 neutropenia compared to earlier lines of therapy. Inhibition of cyclin dependent kinases 4 and 6 (CDK 4/6) with palbociclib will have efficacy in combination with fulvestrant or tamoxifen in patients whose tumors have been previously exposed to chemotherapy. Palbociclib at 100 mg will result in similar inhibition of phospho-RB and reduction in Ki67 as palbociclib at 125 mg measured in tumor and skin. Inhibition of RB phosphorylation will be similar in skin and tumor. Inhibition of phospho-RB will correlate with progression free survival (PFS) Circulating plasma tumor DNA (ptDNA) may be useful for evaluation of ER mutations and help with further understanding hormone resistance
Primary Objective	To evaluate the incidence of grade 3/4 neutropenia in patients with HR+ advanced breast cancer previously exposed to chemotherapy treated with fulvestrant or tamoxifen in combination with 100 mg or 125 mg of palbociclib pathway
Secondary Objectives	• To evaluate progression-free survival with 100 mg and 125 mg dosing of palbociclib • To evaluate inhibition of RB phosphorylation in tumor and in skin at 100 mg and 125 mg dosing of palbociclib. • To evaluate the correlation between inhibition of RB phosphorylation in skin and tumor. • To evaluate the correlation between inhibition of RB phosphorylation and PFS • To evaluate the response and clinical benefit rate of 100 mg and 125 mg dosing of palbociclib • To evaluate the toxicity associated with 100 mg and 125 mg dosing of palbociclib given in combination with fulvestrant or tamoxifen To evaluate markers of resistance to palbociclib and fulvestrant or tamoxifen in ptDNA

Study Design	Approximately 70 patients with HR+ advanced breast cancer will be enrolled. All patients will receive either fulvestrant (500 mg IM on days 1 and 15 in the first 28 days, then every 28 days thereafter) or tamoxifen (20 mg PO daily by physician choice). Pre-menopausal women must be in chemical menopause. Arm 1 will receive palbociclib 100 mg qd, days 1-21 every 28 days. Arm 2 will receive palbociclib 125 mg qd, days 1-21 every 28 days. Restaging will be performed every 8 weeks. Therapy will be continued until PD or unacceptable toxicity. Patients will be randomly allocated in a 1:1 ratio to take either 100 mg or 125 mg of palbociclib. Randomized treatment assignments will be made by permuted blocks within stratum defined by stratified by choice of endocrine therapy (tamoxifen versus fulvestrant).
Number of patients	70 patients; 35 will be allocated to arm 1 and 35 will be allocated to arm 2
Duration of Therapy	In the absence of treatment delays due to adverse events, treatment will continue until: • Disease progression • Inter-current illness that prevents further administration of treatment • Unacceptable adverse event(s) • Patients decides to withdraw from the study • Significant patient non-compliance with protocol
Duration of Follow up	Patients will be followed 30 days post study drug discontinuation. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower. Patients continuing fulvestrant or tamoxifen but who have discontinued palbociclib for any reason other than disease progression will continue with the regular trial schedule until disease progression.
Study Drugs	**Palbociclib: 100 mg or 125 mg** Palbociclib is an oral CDK 4/6 inhibitor with potential antineoplastic activity. **Tamoxifen: 20 mg** Tamoxifen is an oral selective estrogen receptor modulator (SERM). **Fulvestrant: 50 mg/mL solution, given as a 500 mg IM injection** Fulvestrant is a selective estrogen receptor down-regulator (SERD) given by intramuscular (IM) injection.
Safety Assessments	Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.03.

List of Abbreviations

AE	adverse event
AI	aromatase inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CDK 4/6	cyclin dependent kinase 4/6
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCT	Hematocrit
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	Hemoglobin
HR+	hormone receptor positive
HIV	human immunodeficiency virus
IM	intramuscular
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	Intravenous
LDH	lactate dehydrogenase

List of Abbreviations

LFT	liver function test
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
Palbo	palbociclib
PD	progressive disease
PI3K	phosphotidyl inositol 3 kinase
PFS	progression free survival
PK	Pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
QOL	Quality of Life
RB	Retinoblastoma
RBC	red blood cell (count)
SERD	selective estrogen receptor downregulator
SERM	selective estrogen receptor modulator
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal
WBC	white blood cell (count)

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1 Objectives of the Study

1.1 Primary

- To evaluate the incidence of grade 3/4 neutropenia in patients with HR+ advanced breast cancer previously exposed to chemotherapy, treated with fulvestrant or tamoxifen in combination with palbociclib at a dose of 100mg or 125mg.

1.2 Secondary

- To evaluate progression-free survival with 100 mg and 125 mg dosing of palbociclib
- To evaluate inhibition of RB phosphorylation in tumor and in skin at 100 mg and 125 mg dosing of palbociclib.
- To evaluate the correlation between inhibition of RB phosphorylation in skin and tumor.
- To evaluate the correlation between inhibition of RB phosphorylation and PFS
- To evaluate the objective response and clinical benefit rate of palbociclib given at 100 mg or 125 mg.
- To evaluate the toxicity associated with palbociclib given at 100 mg and 125 mg in combination with fulvestrant or tamoxifen
- To evaluate markers of resistance to palbociclib and fulvestrant or tamoxifen in circulating plasma tumor DNA (ptDNA).

2 Introduction

2.1 Hormone Receptor Positive Breast Cancer

Hormone receptor positive (HR+) breast cancer is the most commonly diagnosed subset of breast cancer, and affects thousands of patients every year. Endocrine therapy is highly effective for this subset of breast cancer, and standard adjuvant management for postmenopausal women with HR+ breast cancer includes adjuvant endocrine therapy for at least 5 years, including treatment with an aromatase inhibitors. Despite this effective therapy, a percentage of patients will relapse with incurable metastatic disease, likely related to the development of resistance to endocrine therapy[1]. Therefore, improving the efficacy of adjuvant endocrine therapy would be of great benefit to a large number of breast cancer patients, and is an unmet medical need.

A variety of novel agents are in development to improve the efficacy of endocrine therapy against HR+ breast cancer. One pathway of interest is the PI3K/mTOR pathway, and agents targeting this pathway, including everolimus, have demonstrated efficacy in combination with either aromatase inhibitors or tamoxifen when treating endocrine-resistant metastatic HR+ breast cancer[2,3]. Cell cycle inhibition is another target of choice, forming the biological motivation for the proposed trial.

Postmenopausal women with HR+/HER2-negative breast cancer that have progressed after treatment with letrozole or anastrozole are now able to receive everolimus (Affinitor) in combination with exemestane. However, despite promising efficacy recently demonstrated in the BOLERO-2 trial in ER+/HER2-negative patients (median PFS 7.8 months for the everolimus-exemestane combination vs. 3.2 months for exemestane alone per investigator's assessment), a high percentage of patients discontinued everolimus due to a challenging tolerability profile[2,4]. Overall survival was improved by 4 months, although this was not statistically significant (30.98 vs 26.55 months, p=.14)[5]. Toxicity remains a world-wide

challenge for the use of everolimus in breast cancer. New options for improving response to hormone therapy are clearly needed.

2.2 Palbociclib Mechanism of Action

Palbociclib is an orally active pyridopyrimidine, first-in-class compound that is a potent and highly selective reversible inhibitor of cyclin-dependent kinase (CDK) 4/6[6]. The compound prevents cellular deoxyribonucleic acid (DNA) synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials[7,8]. There is a strong link between the action of estradiol and the G1-S phase transition, where it drives transcriptional activation of cyclin D1 leading to formation of the cyclin D1-CDK4/6-Rb complex which facilitates the G1 to S phase transition. Preclinical data suggest that estrogen resistant models are highly sensitive to the combination of palbociclib with anti-hormonal therapy or palbociclib alone[9].

Blockade of the estrogen receptor (ER) signaling pathway is synergistic with cell cycle arrest induction, as demonstrated by the more than doubling in median progression free survival (PFS) observed to date in a phase II trial evaluating patients with ER+ metastatic breast cancer treated with the combination of an aromatase inhibitor (AI) and palbociclib compared with aromatase inhibitor alone[10]. Overcoming resistance to endocrine therapy in breast cancer patients is a major challenge and there is a high unmet need for safe and efficacious treatment options in women resistant to endocrine therapy.

Palbociclib preclinical data indicate that mechanisms of action include direct effect on growth arrest as well as potential secondary cytoreductive activity. Single agent palbociclib has showed antiproliferative effects (selective G1 arrest) on Rb-positive cancer cells in vitro and in vivo34 where palbociclib activity was associated with reduced Rb-phosphorylation and decreased expression of the cell proliferation marker Ki67. Palbociclib showed no activity in Rb-negative tumor cell xenografts, consistent with CDK4/6 inhibition as the sole mode of action[11].

Palbociclib was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to palbociclib (IC50 <150 nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell lines show the opposite characteristics. Sensitive cell lines in this panel represent mostly the luminal ER+ subtype[9]. A phase I trial tested 3 dose levels of palbociclib in patients with solid tumors, enrolling 41 patients at three dose levels, with drug given for 21 days out of every 28 days[12]. The dose limiting toxicity was neutropenia, with a recommended phase II dose of 125 mg. Clinical benefit with objective response was seen in 10 (27%) for at least 4 cycles, and in 6 patients for at least 10 cycles, one of whom had breast cancer. Other than neutropenia, which was proportionate to drug exposure, palbociclib was well tolerated.

A Phase 2 study was conducted with single agent palbociclib in 37 women with advanced breast cancer, of whom 89% had HR+ disease[13]. Palbociclib was given at 125 mg orally, Days 1- 21 of a 28-day cycle. Over 90% had prior chemotherapy for metastatic disease; 84% had prior hormonal therapy. Clinical benefit was seen in 7 out of the 37 patients, and only in those with HR+ disease for a rate in that subpopulation of 21%. The overall response rate was just 6% in HR+ disease. Grade 3/4 toxicity included neutropenia in 54%, thrombocytopenia in 19%, and grade 1/2 fatigue in 70%.Translational studies examining molecular predictors of response are in progress. .

Combinations with hormone therapy are well tolerated. The combination of palbociclib with tamoxifen has been tested in vitro in ER+ human breast cancer cell lines indicating a synergistic interaction and provided a biologic rationale for evaluating the combination of palbociclib with anti-hormonal therapy in the clinic[14]. Also, recent data in hormone resistant models (MCF7-CYP19) indicate a significant benefit of the combination of palbociclib and letrozole as well as palbociclib and fulvestrant over single agents of letrozole and fulvestrant (Pfizer, Investigational Brochure, Version Dec 2013).

Encouraging Phase 2 data in a patient population of ER+/HER2-negative postmenopausal patients with newly diagnosed metastatic breast cancer indicate that the addition of palbociclib to letrozole significantly extends PFS with a tolerable safety profile[10] .The results of two interim analyses showed a consistent trend of clinically meaningful improvements in PFS. In the first interim analysis (Part 1; N=66), the median PFS for the palbociclib plus letrozole arm was 18.2 months versus 5.7 months for the letrozole alone arm (HR=0.35; 95% CI: 0.17, 0.72; p=0.006). The second interim analysis (N=165) demonstrated a statistically significant improvement in PFS (26.1 vs. 7.5 months, respectively; HR=0.37; 95% CI: 0.21, 0.63; p <0.001)[15] . Final analysis of this study confirmed the interim analysis results[10].With 60% of events recorded, median PFS for palbociclib plus letrozole was 20.2 months versus 10.2 months for the letrozole alone arm (HR=0.49; 95% CI: 0.32, 0.75; p = 0.0004). Overall response was increased at 43% with the combination compared to 33% in those receiving letrozole. There was no difference in overall survival (37 vs 33 months respectively). This data led to accelerated approval of palbociclib in combination with letrozole as first-line therapy for advanced breast cancer in February of 2015.

Two placebo controlled phase III trials have recently completed accrual, in the first-line (Paloma 2, with letrozole) and later-line (Paloma 3, with fulvestrant) hormone sensitive settings. The phase II and phase III trials have included patients whose disease had relapsed at various time points after prior endocrine therapy. Paloma 3 reported an improvement in PFS with the combination of fulvestrant and palbociclib compared to fulvestrant alone in the Paloma 3 trial[16]. This data was presented at the American Society of Clinical Oncology meetings in June of 2015 and published on the same day[17]. The median progression-free survival was 9.2 months (95% confidence interval [CI], 7.5 to not estimable) with palbociclib–fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo–fulvestrant (hazard ratio for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001). The most common grade 3 or 4 adverse events in the palbociclib–fulvestrant group were neutropenia (62.0%, vs. 0.6% in the placebo–fulvestrant group), leukopenia (25.2% vs. 0.6%), anemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Thirty-three percent of patients had received one line of prior chemotherapy in the advanced stage setting, but little data is available regarding duration of therapy or impact of prior chemotherapy on toxicity. In addition, patients in this trial could not have received inhibitors of the PI3K pathway including the approved mTOR inhibitor everolimus[17]. Patients with hormone receptor positive disease and prior exposure to chemotherapy in the metastatic setting, whether already treated with everolimus or a PI3K inhibitor or not have very few options for therapy. This will become even more acute when adjuvant and first-line trials are enrolling patients. Presumably the mechanism of resistance to PI3K inhibitors and CDK/cell cycle inhibition is non-overlapping, but this has not been studied to date. Many patients in the metastatic setting will have received prior chemotherapy as both adjuvant and metastatic treatment. In these patients, bone marrow reserve may limit the tolerability of CDK inhibition. Exploring the activity of CDK inhibition in combination with hormone therapy in patients with prior exposure to agents targeting different pathways, and in those with prior chemotherapy, is an important and timely investigation. This study also allows us to study lower dose palbociclib with pharmacodynamics markers.

Palbociclib is well tolerated but neutropenia is a significant complication[12] leading to dose reductions and delays, with grade 3 and 4 neutropenia combined occurring in 54% of patients, although the majority was grade 3 (48%). Cycle delays occurred in 45%, dose interruptions in 33%, and dose reductions in 40%. In the adjuvant setting, this could be a significant problem, requiring multiple visits and possible use of growth factors, particularly as these patients will have often just completed adjuvant or neoadjuvant chemotherapy. It would be helpful to have a surrogate marker of efficacy in order to more efficiently study lower doses of the CDK inhibitor. Palbociclib is a potent inhibitor of RB phosphorylation, and this effect has been demonstrated in mantle cell lymphoma (MCL) tumor samples before and after treatment. In a pharmacodynamic study of the selective CDK4/6 inhibitor PD0332991 (palbociclib), conducted in 17 patients with relapsed disease. Five patients achieved progression-free survival time of > 1 year (range, 14.9-30.1+ months), with 1 complete and 2 partial responses (18% objective response rate;

90% confidence interval, 5%-40%). The results of the study confirmed CDK4/6 inhibition by PD0332991 at a well-tolerated dose and schedule and suggest clinical benefit in a subset of MCL patients[18].

2.3 Rationale

We propose to evaluate the incidence of grade 3/4 neutropenia of palbociclib at two different doses combined with fulvestrant or tamoxifen in patients with previous exposure to chemotherapy for advanced disease. The combination with fulvestrant or tamoxifen is well suited to this patient population. There are few ongoing trials combining CDK inhibition with tamoxifen, and allowing the option to receive fulvestrant will increase options for previously treated patients. We also propose to evaluate inhibition of phospho-RB in breast cancer at 100 mg and 125 mg of palbociclib in tumor and skin in patients enrolled on this trial. Patients will be allocated to receive either 100 mg or 125 mg at study start. If inhibition of phosphorylation in skin correlates with the findings in tumor, this could represent an important surrogate marker of anti-tumor effect. Comparing the extent of inhibition at 100 mg and 125 mg will provide information about the ability of the two doses to effectively reach their intended target. Biopsies will be performed at baseline and after 14-21 days of therapy in cycle one. Steady state occurs after 7-10 days of treatment, so this should provide an accurate representation of drug effect. Patients whose disease is progressing on 100 mg may, at physician discretion, escalate to 125 mg before stopping study therapy.

Recent data has illuminated the role of mutations in the estrogen receptor in resistance to hormone therapy. We will collect plasma DNA for future study of these mutations.

2.4 Hormone Therapy

Tamoxifen

Tamoxifen is the most commonly used selective estrogen receptor modulator (SERM). It is currently used in the prevention of breast cancer, to treat ductal carcinoma in situ, and to treat HR+ invasive breast cancer in the early and advanced stage settings. Tamoxifen is generally well tolerated and due to its extensive use, its toxicities and long-term sequelae are well characterized. Women treated with tamoxifen may experience flushing (similar to the flushing women experience during menopause), vaginal dryness and vaginal discharge. The most serious side effect is the slightly increased risk of thromboembolic events. In a trial involving 900 women treated with either tamoxifen or letrozole, 9 out of 455 patients experienced a thromboembolic event (2%), compared to 3 patients out of 455 in the group treated with letrozole (<1%). Other side effects included hot flashes (25%), headaches (5%), fatigue (5%) and nausea (8%)[19]. The occurrence of endometrial cancer (<0.5%) has been predominantly observed when tamoxifen is used in the preventive or adjuvant setting[20]. Hence, the cumulative administration of tamoxifen is rarely hampered by toxicity but rather by the emergence of resistance suggested by clinical progression while on the drug.

Multiple enzymes are responsible for the metabolism of tamoxifen and its active metabolites including CYP3A4, CYP2C9, and CYP2D6. In vitro evidence suggests that tamoxifen and one of its primary active metabolites, 4-hydroxy-tamoxifen, are inducers of CYP3A4 enzymes. In clinical trials, co-administration of tamoxifen with letrozole and anastrozole (both CYP3A4 substrates) has resulted in decreased exposures of each by 37% and 27%, respectively. Palbociclib is aCYP3A4 substrate and CYP3A4 is thought to be the primary route of the oxidative metabolism of palbociclib, thus, the co-administration of tamoxifen and palbociclib may lead to lower circulating levels of palbociclib and require an upward dose adjustment in palbociclib if these two compounds are used in conjunction. Additionally, time-dependent inhibition of CYP3A4 has been observed in preclinical studies of palbociclib[21].

A fixed-sequence 2-period crossover drug-drug interaction (DDI) study to assess the effect of steady-state levels of tamoxifen and its active metabolites on the pharmacokinetics of single

dose palbociclib in healthy volunteers has been conducted to rule out a need for palbociclib dose-adjustments when used in conjunction with tamoxifen. There was no evidence of a clinically significant pharmacokinetic interaction in this trial[22]

Fulvestrant

Fulvestrant is a selective estrogen receptor down-regulator (SERD) with an affinity for ER comparable to estradiol. It blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity, and is currently indicated for the treatment of HR+ metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

The mechanism of action is associated with down-regulation of ER protein levels. Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down-regulates ER protein in ER-positive tumors compared with placebo. There was also a significant decrease in progesterone receptor (PR) expression consistent with a lack of intrinsic estrogen agonist effects. It has also been shown that fulvestrant 500 mg/month downregulates ER and the proliferation marker Ki67 to a greater degree than fulvestrant 250 mg/month in breast tumors in postmenopausal neoadjuvant setting[23].

Two Phase 3 clinical trials were completed in a total of 851 postmenopausal women with advanced breast cancer (77% of the women were ER+), who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. These trials compared the safety and efficacy of monthly administration of fulvestrant at the lower dose of 250 mg versus the daily administration of 1 mg of the AI anastrozole. Monthly 250 mg fulvestrant was at least as effective as anastrozole in terms of PFS, OR, and time to death. The combined data showed an objective response rate for fulvestrant 250 mg of 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with fulvestrant and 27.6 months for patients treated with anastrozole. The hazard ratio of fulvestrant 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19)[24, 25].

There is evidence to suggest that doses of fulvestrant higher than 250 mg may have greater pharmacodynamic activity against the ER pathway, and 500 mg dosing with an initial load is now the standard of care and is FDA approved. A Phase 3 clinical trial (CONFIRM) was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during anti-estrogen (AE) therapy (AE subgroup) and 313 patients whose disease had recurred or progressed during aromatase inhibitor (AI) therapy (AI subgroup). This trial compared the efficacy and safety of fulvestrant 500 mg (n=362) with those of fulvestrat 250 mg (n=374). PFS for fulvestrant 500 mg was 6.5 months compared to 5.5 months for fulvestrant 250 mg. Overall survival data from the time of final analysis showed a median time to death of 26.4 months for fulvestrant 500 mg versus 22.3 months for fulvestrant 250 mg (HR (95%CI) 0.81 (0.69, 0.96), p-value 0.016)[26]. Also, a pilot Japanese study showed fulvestrant 500 mg to have clinical activity in the treatment of advanced or recurrent breast cancer, to be well tolerated, and to result in plasma levels approximately double those seen with 250 mg fulvestrant[27].

The potential for a clinically significant drug-drug interaction between palbociclib and fulvestrant is very low. The routes of elimination for fulvestrant include combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, conjugate with glucuronic acid and/or sulphate. There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 in vitro, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme.

Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the PK of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP3A4, indicated that ketoconazole had no effect on the PK of fulvestrant and dosage adjustment is not necessary in patients with co-prescribed CYP 3A4 inhibitors or inducers. A phase III trial has completed accrual, with an initial safety assessment with trough plasma concentrations demonstrating no pharmacokinetic interactions between fulvestrant and palbociclib[28].

2.5 Hypotheses

- Inhibition of CDK 4/6 with palbociclib in combination with fulvestrant or tamoxifen in patients exposed to 1-3 lines of prior chemotherapy for advanced disease will be well tolerated, with similar rates of neutropenia as less-heavily pre-treated patients.
- Inhibition of CDK 4/6 with palbociclib in combination with fulvestrant or tamoxifen in heavily pre-treated patients with advanced breast cancer will improve expected response and progression free survival compared to hormone therapy alone
- Palbociclib at 100 mg will result in similar inhibition of phospho-RB and reduction in Ki67 as palbociclib at 125 mg as assessed in tumor and skin.
- Inhibition of RB phosphorylation will be similar between tumor and skin.
- Inhibition of phospho-RB will correlate with PFS
- Circulating tumor DNA may be useful for evaluation of ER mutations and help with further understanding hormone resistance

2.6 Correlative Study 1: Evaluation of PD markers in tumor and skin.

Tissue samples will be procured from tumor and skin at baseline and between days 14-21 of the first cycle of palbociclib. In addition, an optional biopsy at the time of progression should be obtained if possible. Tumor will be procured by core biopsy (18 gauge) or fine needle aspirate. A skin tumor biopsy is allowable for the tumor biopsy. For skin tumor biopsies, at least two 3mm or one 5mm punch biopsy should be obtained. For the non-tumor skin biopsy, 3 mm should be obtained. Formalin-fixed, paraffin-embedded samples will be assessed for standard histology with H&E staining and subjected to immunohistochemistry for total Rb (BD Pharmingen), phospho-Rb [pS807/S811] (Cell Signaling Technology); phospho-Rb [pS780] (Cell Signaling Technology) and Ki-67 (DaKo). TUNEL staining will also be performed (ApopTag Peroxidase in Situ Apoptosis Detection Kit). Image quantification will be performed using TissueQuest software (Tissue Gnostics). Immunohistochemistry and image quantification will be performed in the Specialized Histopathology Core at the Brigham and Women's Hospital under the direction of Dr. Scott Rodig, and supervised by Dr. Geoff Shapiro.

2.6.1 Correlative Study 1 Background

Based on the experience in Mantle Cell Lymphoma[18], a > 85% reduction in expression of phospho-Rb and Ki-67 occurred in patients who achieved long term disease control (i.e. > 1 year without disease progression). This study also evaluated fluorothymidine-PET scans as a non-invasive measure of G1 arrest; a > 70% reduction in summed FLT SUVmax was seen in patients who achieved long term disease control. All of these parameters were considered biologically to be measuring a similar parameter—cell cycle arrest as a consequence of CDK4/6 inhibition. Based on this data, we believe that if we had > 70% reduction in the parameter to be measured (Rb in skin), would be reasonable to assume "positive proof of mechanism.

Meaningful assessments and correlations among parameters were achieved with 10 paired tumor biopsies assessed for total and phospho-Rb staining and 15 paired tumor biopsies

assessed for Ki-67 staining. The degree of reduction in phospho-Rb and/or Ki-67 staining needed to predict favorable long term outcome when palbociclib is administered with hormonal therapy for breast cancer is unknown. For this study, at each of the 100 mg and 125 mg dose levels, a > 70% reduction in these parameters in at least 75% of the evaluated samples will be a priori defined as proof-of-mechanism in tumor or skin.

2.7 Correlative Study 2: Exploratory analysis of markers of endocrine resistance in circulating plasma tumor DNA.

Circulating plasma will provide a novel source of tumor DNA that will allow identification of markers of endocrine resistance such as mutations in the ER

This is an exploratory endpoint. All patients enrolled in this trial will have whole blood for circulating ptDNA collected at study entry.

2.8 Endpoints

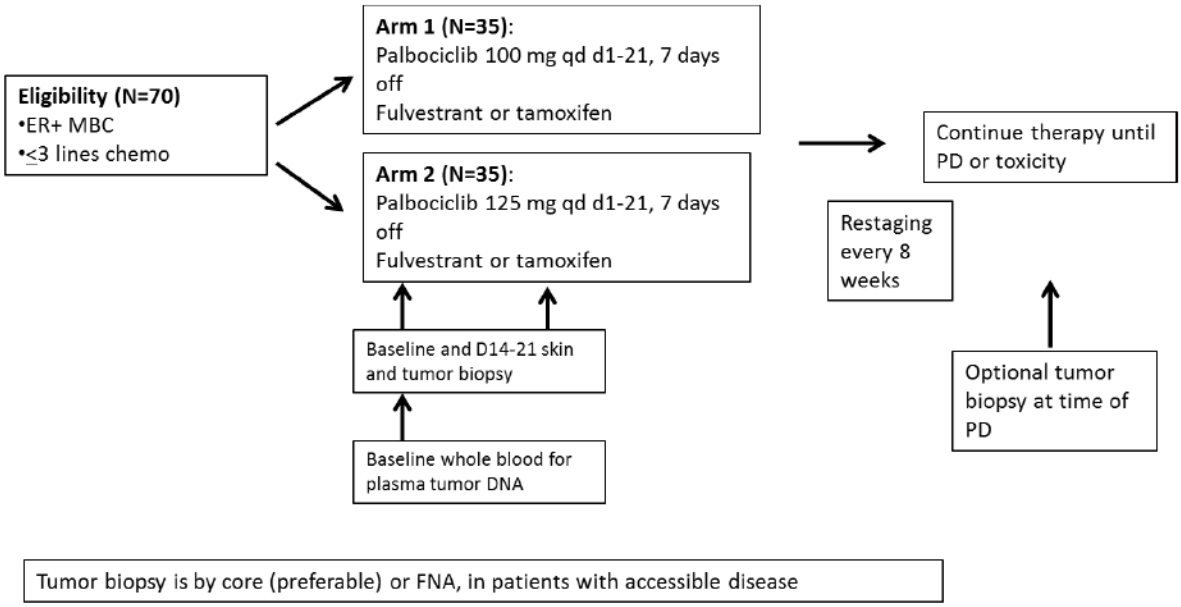
2.8.1 Primary Endpoints

- Grade 3/4 neutropenia as defined by CTCAE v4.03 in patients with prior exposure to 1-3 lines of chemotherapy for metastatic breast cancer receiving 125 and 100 mg of palbociclib in combination with tamoxifen or fulvestrant.

2.8.2 Secondary and Exploratory Endpoints

- Progression free survival (PFS), defined as the interval from study entry to the first documented evidence of disease progression by RECIST 1.1. Patients who remain event-free at the time of analysis will be censored at their last date of follow-up.
- Objective response (CR+PR) and clinical benefit (CR+PR+SD>24wk) by RECIST 1.1
- Measurement of the inhibition of RB phosphorylation in tumor and in skin
- Preliminary correlation of RB inhibition with toxicity and efficacy
- Evaluate exploratory markers in circulating plasma tumor DNA (ptDNA)

3 Study Design



Patients progressing on 100 mg after at least one month on therapy can, at physician discretion, escalate to 125 mg of palbociclib while continuing their hormone therapy to evaluate for response. If a subsequent scan shows further progression, study therapy must be discontinued.

3.1 Characteristics

Eligible patients will receive either fulvestrant or tamoxifen, by physician and patient preference. In addition, patients will be allocated to receive either 100 mg or 125 mg daily for 3 out of every 4 weeks. Patients with disease clearly progressing on either agent should receive the alternate hormone therapy.

All patients with accessible sites of disease will undergo tumor biopsies at baseline and at 14-21 days. All patients regardless of accessible tumor will undergo skin biopsies at baseline and at 14-21 days.

Patients will be asked to undergo an optional tumor biopsy at the time of progression to analyze markers of resistance to CDK 4/6 inhibition.

3.2 Number of Subjects

The target enrollment is a total of 70 treated patients. Based on the data from Paloma 1 and 3, we have defined an unacceptable rate of neutropenia as 63.6% of the treated population. This corresponds to the upper bound of a 90% confidence interval from the rate reported in PALOMA-1: 45 (54%) of 83 patients (90% CI: 44.6% to 63.6%). With 35 patients treated at each dose level, there is 78% power to reject the null if the true rate is 43.6% (Δ = 20.0%) when controlling the one-sided Type I alpha at 0.05 for each test.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained

from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.

2. Female or male patients 18 years of age or older

3. Female patients should be either:

    - Postmenopausal, as defined by at least one of the following criteria:
    - Age ≥60 years;
    - Age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause;
    - Documented bilateral oophorectomy;
    - Medically confirmed ovarian failure.

    OR

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

4. Documentation of ER-positive and/or PR-positive tumor (≥1% positive stained cells) based on most recent tumor biopsy (unless bone-only disease, discuss with the Study Chair if results in different biopsies are discordant in terms of hormone receptor positivity) utilizing an assay consistent with local standards.

5. Documented HER2-negative tumor based on local testing on most recent tumor biopsy: HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.

6. Must have received at least one but no more than 3 lines of chemotherapy for advanced breast cancer.

    - Patients who have developed metastatic disease on adjuvant hormone therapy within 24 months of completing adjuvant chemotherapy are considered to have had one line of chemotherapy and are eligible for this trial.

7. Prior treatment with an mTOR inhibitor or PI3K inhibitor is allowed but not required.

8. Any number of lines of prior hormone therapy are allowed

    - Patients with clear progression on either tamoxifen or fulvestrant should receive the alternate agent if feasible. If a patient has received both agents in the past, the drug received while on study is at the discretion of the treating physician.

9. Ability to have a skin and tumor biopsy from any site. Patients without accessible tumor for biopsy will be considered on a case by case basis.

    - Patients who cannot be biopsied will not be replaced (although up to 5 ineligible/inevaluable patients can be replaced)
    - Patients without accessible tumor for biopsy must provide archived tumor from the most recent biopsy available

10. Bone marrow, hepatic, and renal function as follows:

    Adequate bone marrow function:

    - leukocytes ≥ 2500/mL
    - absolute neutrophil count ≥ 1,000/mL
    - platelets ≥ 100,000/mL"

    Adequate hepatic function:

    - total bilirubin within normal institutional limits (unless Gilbert's disease with elevated indirect bilirubin only)
    - AST(SGOT) ≤ 2.5 X institutional upper limit of normal
    - ALT(SGPT) ≤ 2.5 X institutional upper limit of normal"
    - Adequate renal function:
    - creatinine Within or belownormal institutional limits

11. Measurable or evaluable disease as defined by RECIST version 1.1. Tumor lesions previously irradiated or subjected to other loco-regional therapy will only be deemed measurable if progression at the treated site after completion of therapy is clearly documented.

12. Eastern Cooperative Oncology Group (ECOG) performance status 0-1

13. Resolution of acute toxic effects of prior therapy or surgical procedures to National Cancer Institute (NCI) CTCAE Grade ≤1 (except alopecia)

14. Ability to understand a written informed consent document, and the willingness to sign it

15. Effective birth control should be utilized as indicated.

3.3.2 Exclusion Criteria

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

1. Prior treatment with any CDK inhibitor.

2. Patients with advanced/metastatic, symptomatic, visceral spread, at risk of life-threatening complications in the short term by investigator assessment.

3. Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.

4. Current use of food or drugs known to be potent CYP3A4 inhibitors, drugs known to be potent CYP3A4 inducers. See prohibited meds in appendix 5.

5. Major surgery, chemotherapy, radiotherapy, or other anti-cancer therapy within 2 weeks before randomization. Note: No washout required for single dose Gamma Knife radiation.

6. Any other malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, or localized papillary carcinoma of the thyroid.

7. QTc interval >480 msec, family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes.

$$\text{QTc (Bazett)} = \frac{QT}{\sqrt{RR}}$$

8. Any of the following within 6 months prior to study enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, symptomatic congestive heart failure, or cerebrovascular accident excluding transient ischemic attack.

9. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of palbociclib, such as history of GI surgery with may result in intestinal blind loops and patients with clinically significant gastroparesis, short bowel syndrome, unresolved nausea, vomiting, active inflammatory bowel disease or diarrhea of CTCAE v4.03 Grade >1.

10. Prior hematopoietic stem cell or bone marrow transplantation.

11. Abnormalities in coagulation such as bleeding diathesis, or treatment with anticoagulants (that cannot be safely held for biopsy) that would preclude tumor and skin biopsies.
    - For fulvestrant: Ongoing anticoagulation that would preclude an IM injection
    - For tamoxifen: Documented hypercoagulable state not receiving anticoagulation

12. Known or possible hypersensitivity to palbociclib (CTCAE v4.03).

13. Known human immunodeficiency virus infection.

14. Other severe acute or chronic medical or psychiatric condition, including recent or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

15. Participation in other studies involving investigational drug(s) (Phases 1-4) within 2 weeks before randomizationin the current study.

16. Women should not become pregnant or breastfeed while on this study.

3.3.3 Inclusion of Underrepresented Populations

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards race in the clinical trial outlined. This trial is open to the accrual of men and women.

3.4 Duration of Therapy

Treatment will continue until participation and study therapy is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to:

- Disease progression
- The occurrence of an adverse event or a concurrent illness
- A patient's request to end participation
- A patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent.
- There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

3.5 Duration of Follow Up

Patients will be followed 30 days post study drug discontinuation. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower. Patients continuing fulvestrant or tamoxifen but who have discontinued palbociclib for any reason other than disease progression will continue with the regular trial schedule until disease progression.

3.6 Randomization Procedures

Patients will be randomly allocated in a 1:1 ratio to take either 100 mg or 125 mg of palbociclib. The assignments will be made by permuted blocks within stratum defined by endocrine therapy: fulvestrant or tamoxifen. Randomization tables will be generated by our collaborating statistician at Dana-Farber Cancer Institute using the in-house software RANSCH developed by the Eastern Cooperative Oncology Group Statistical Center.

3.7 Registration Procedures

All subjects must be registered through the Hoosier Cancer Research Network (HCRN) electronic data capture (EDC) system. A subject is considered registered when an 'On Study' date is entered into the EDC system.

Subjects must be registered and randomized prior to starting protocol therapy. Following registration and randomization, eligible participants should begin protocol treatment within 2 weeks. Issues that would cause treatment delays should be discussed with the Protocol Chair. If a participant does not receive protocol therapy following randomization within the allowed time period, the participant will become ineligible and will be cancelled from the study. Such patients will have to undergo screening again to participate in the study.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Investigational Drug Palbociclib

Palbociclib is available in 75, 100 mg and 125 mg capsules/tablets for oral administration.

Classification

Palbociclib is a cyclin-dependent kinase 4/6 (CDK) inhibitor with potential antineoplastic activity.

Mechanism of Action

Palbociclib selectively inhibits cyclin-dependent kinase 4 (CDK4) and 6 (CDK6), thereby inhibiting retinoblastoma (Rb) protein phosphorylation early in the G1 phase leading to cell cycle arrest. This suppresses DNA replication and decreases tumor cell proliferation. CDK4 and 6 are serine/threonine kinases that are upregulated in many tumor cell types and play a key role in the regulation of cell cycle progression.

Metabolism

To date, pharmacokinetic data have been collected in 4 clinical studies for a total of 138 cancer patients. The exposure and Cmax) increased in a dose proportional manner over the dose range of 25 to 225 mg once daily (QD) following palbociclib administration on Days 1 and 8 of Cycle 1, although some variability (low to moderate) around these doses was observed particularly at the 150 mg QD dose level. Following repeated daily dosing to Day 15 and Day 21 (assumed to be steady state), palbociclib was absorbed with a median Tmax of ~4 hours. The mean palbociclib Vz/F was 3103 L, which is significantly greater than total body water (42 L), indicating that palbociclib extensively penetrates into peripheral tissues.

Palbociclib was eliminated slowly; the mean $t_{1/2}$ was 26.5 hours (ranged 15.8 to 36.2 hours) and the mean CL/F was 86.1 L/hour. Palbociclib accumulated following repeated dosing with a median Rac of 2.4, which is consistent with a half-life of ~27 hours.

Preliminary results from the recently performed food effect study (A5481021) suggested that the administration of palbociclib with food results in more consistent drug absorption and exposure than administration of palbociclib in a fasted state. As a result of these findings, patients should be instructed to take palbociclib with food.

Storage and handling

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

Side Effects

The most frequently reported treatment-related adverse events included neutropenia, leukopenia, anemia, and fatigue.

A phase 2 study of palbociclib showed toxicities that were mostly Grade 1/2, and Grade 3/4 toxicities were limited to transient neutropenia (50%) and thrombocytopenia (21%). A large phase II study of palbociclib combined with letrozole found a 54% rate of grade 3/4 neutropenia but no increase in febrile neutropenia. Neutropenia was easily managed with dose delay and dose reduction.

How Supplied

Pfizer, Inc. will supply palbociclib at no charge to subjects participating in this clinical trial.

Complete and updated adverse event information is available in the Investigational Drug Brochure

4.1.2 Tamoxifen

Tamoxifen is available in the following doses for oral administration in 20 mg Tablets. Each tablet contains 30.4 mg of tamoxifen citrate, which is equivalent to 20 mg of tamoxifen.

Classification

Non-steroidal anti-estrogen

Mechanism of Action

Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 ng/mL (range 35 to 45 ng/mL) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination half-life of about 5 to 7 days. The average peak plasma concentration of N-desmethyl tamoxifen is 15 ng/mL (range 10 to 20 ng/mL). Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/mL (range 67-183 ng/mL) for tamoxifen and 336 ng/mL (range 148-654 ng/mL) for N-desmethyl tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for 3 months are 122 ng/mL (range 71-183 ng/mL) and 353ng/mL (range 152-706 ng/mL), respectively.

After initiation of therapy, steady state concentrations for tamoxifen are achieved in about 4 weeks and steady-state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite. In a steady state, crossover study of 10 mg NOLVADEX tablets given twice a day vs. a 20 mg NOLVADEX tablet given once daily, the 20 mg NOLVADEX tablet was bioequivalent to the 10 mg NOLVADEX tablets.

Metabolism

Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.

Excretion

Studies in women receiving 20 mg of 14C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as the primary route of elimination. The drug is excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

Drug-drug Interactions

In vitro studies showed that erythromycin, cyclosporine, nifedipine and diltiazem competitively inhibited formation of N-desmethyl tamoxifen with apparent K1 of 20, 1, 45 and 30 μM, respectively. The clinical significance of these in vitro studies is unknown.

How Supplied

Commercial supplies of tamoxifen (generic) will be used in this study and billed to third party payers or to the subject. (AstraZeneca has discontinued the commercial manufacture and distribution of branded NOLVADEX® tablets in the United States as of June 2006)

Contraindications

Tamoxifen is contraindicated in patients with known hypersensitivity to the drug or any of its ingredients.

Complete and updated adverse event information is available in the Investigational Drug Brochure and product package insert.

4.1.3 Fulvestrant

Fulvestrant is available in 50 mg/mL solution in a single use-vial for intravenous administration.

Classification

An estrogen receptor antagonist indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

Mechanism of Action

Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and downregulates the ER protein in human breast cancer cells.

In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen-resistant, as well as estrogen-sensitive human breast cancer (MCF-7) cell lines. In in vivo tumor studies, fulvestrant delayed the establishment of tumors from xenografts of human breast cancer MCF-7 cells in nude mice. Fulvestrant inhibited the growth of established MCF-7 xenografts and of tamoxifen-resistant breast tumor xenografts.

Fulvestrant showed no agonist-type effects in in vivo uterotropic assays in immature or ovariectomized mice and rats. In in vivo studies in immature rats and ovariectomized monkeys, fulvestrant blocked the uterotrophic action of estradiol. In postmenopausal women, the absence of changes in plasma concentrations of FSH and LH in response to fulvestrant treatment (250 mg monthly) suggests no peripheral steroidal effects.

Metabolism

Biotransformation and disposition of fulvestrant in humans have been determined following intramuscular and intravenous administration of 14C-labeled fulvestrant. Metabolism of fulvestrant appears to involve combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulphate at the 2, 3 and 17 positions of the steroid nucleus, and oxidation of the side chain sulphoxide. Identified metabolites are either less active or exhibit similar activity to fulvestrant in antiestrogen models.

Studies using human liver preparations and recombinant human enzymes indicate that cytochrome P-450 3A4 (CYP 3A4) is the only P-450 isoenzyme involved in the oxidation of fulvestrant; however, the relative contribution of P-450 and non-P-450 routes in vivo is unknown.

Excretion

Fulvestrant was rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Renal elimination was negligible (less than 1%). After an intramuscular injection of 250 mg, the clearance (Mean ± SD) was 690 ± 226 mL/min with an apparent half-life about 40 days.

Contraindications

Fulvestrant is contraindicated in pregnant women, and in patients with a known hypersensitivity to the drug or to any of its components.

Drug-drug Interactions

There are no known drug-drug interactions. Although, fulvestrant is metabolized by CYP 3A4 in vitro, drug interactions studies with ketoconazole or rifampin did not alter fulvestrant pharmacokinetics. Dose adjustment is not needed in patients co-prescribed CYP3A4 inhibitors or inducers.

Storage and handling

Refrigerate, 2°-8°C (36°-46°F). Protect from light, store in the original carton until time of use.

How Supplied

Commercial supplies of fulvestrant (AstraZeneca PLC) will be used in this study and billed to third party payers or to the subject.

Complete and updated adverse event information is available in the Investigational Drug Brochure and product package insert.

4.2 Drug Accountability

The Investigational Pharmacist at each site will manage palbociclib accountability records.

4.3 Drug Ordering

Each site will obtain palbociclib directly from Pfizer as study commercial supply.

4.4 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per institutional standards, adhering to applicable local and federal laws.

5 Treatment Plan

This is a randomized, open label study evaluating the efficacy of two different doses of palbociclib in combination with either fulvestrant or tamoxifen in patients with hormone receptor positive metastatic breast cancer previously treated with inhibitors of the PI3K/mTOR pathway. Serial biopsies of skin and tumor will be evaluated for inhibition of RB phosphorylation.

Each subject will be assigned a unique identification number, which will be used on all case report forms (CRFs) and correspondence regarding the subject.

5.1 Dosage and Administration

Treatment will be administered on an outpatient basis.

Study Drug	Dose	Route	Schedule	Cycle Length
Choice of:				4 weeks (28 days)
Tamoxifen	20 mg	PO	Daily	
Fulvestrant	500 mg	IM	q28days[1]	
Combined with:				
Palbociclib*	100 mg or 125 mg[2]	PO	Daily, day 1-21 q 28 days	

[1]Fulvestrant injections should be given every 28days (+/-7days) with the exception of cycle 1, during which it will be administered on day 1 and day 15.

[2]Arm 1 will receive 100mg dose, Arm 2 will receive 125mg dose

Note: If a patient vomits within 30 minutes of taking Palbociclib, they should re-take the dose. Please ensure the patient documents this properly in their study diary.

5.2 Palbociclib Dose Modifications and Dosing Delays

In the event of significant treatment-related toxicity, palbociclib dosing may be interrupted or delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse sign or symptom.

5.2.1 Palbociclib Dosing Interruptions/Delays

Patients experiencing the following palbociclib related adverse events should have their treatment of palbociclib interrupted or delayed until criteria for retreatment are met:

- Uncomplicated Grade 3 or 4 neutropenia (ANC<1000/mm^3);
- Grade 3 or 4 neutropenia (ANC<1000/mm^3) associated with a documented infection or fever ≥ 38.5°C, 100.4°F;
- Grade 3 or 4 thrombocytopenia (Platelet <50,000/mm^3);
- Grade ≥ 3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment);
- Grade 2 non-hematologic toxicity persisting despite optimal medical treatment and lasting more than 3 weeks;
- Grade 3 QTc prolongation (QTc ≥501 msec on at least two separate ECGs);
- In case of concurrent > 3x ULN ALT and 2x ULN Total Bilirubin, palbociclib will be permanently discontinued.

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

Appropriate follow up assessments should be performed until adequate recovery occurs as assessed by the Investigator Criteria before treatment can resume.

Missed doses are not made up. When the adverse event resolves, the cycle will continue as scheduled. However, if palbociclib start for a specific cycle is delayed for toxicity (neutropenia),

hormone therapy will continue without change. The start of palbociclib will be counted as the date of new cycle start, and drug will be administered for the full 21 day period.

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

5.2.2 Palbociclib Retreatment Criteria

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

- Platelet count ≥ 75,000/mm^3;
- ANC ≥ 1000/mm^3 and no fever;
- Any grade 3 or higher treatment-related and clinically significant non-hematologic AEs considered related to palbociclib have recovered to Grade 1 or baseline.
- Only if treatment was held for QTc prolongation: QTc <480 msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTc remains above 480 msec, cardiology should be consulted and the ECG be monitored more frequently as per the investigator's best medical judgment until QTc ≤480 msec.

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

If the retreatment parameters are met within 3 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Please refer to Dose Reductions Section for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should permanently discontinue palbociclib treatment.

5.2.3 Dose Reductions

Following dose interruption or cycle delay the palbociclib dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for grade 1 or short lasting grade 2 (<3 weeks) treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

In case of a grade 2 toxicity lasting for >3 weeks or a grade 3 toxicity (both assessed in the presence of maximum supportive care as judged by the investigator), dose reduction is recommended for the subsequent cycles. Taking palbociclib according to recommendation (i.e., with food) should be reinforced and confirmed. As needed, dose reduction of palbociclib by one dose level for dosing started at 100mg/d, and by two dose levels for dosing started at 125mg/d (Table 5.1) may be recommended depending on type and severity of the toxicity encountered. Once a dose has been reduced for a given patient, all subsequent cycles should be

administered at that dose level, unless further dose reduction is required. Patients requiring more than 2 dose reductions will be discontinued from the study.

Table 5.1 Dose Modifications and Dosing Delays

Dose Level	Dose of Study Drug
Palbociclib for 3 out of 4 weeks	
Starting dose	125 mg/d
-1	100 mg/d
-2	75 mg/d
	Discontinue Study Treatment

Palbociclib for 3 out of 4 weeks	
Starting dose	100 mg/d
-1	75 mg/d
	Discontinue Study Treatment

Palbociclib recommended dose modifications for treatment-related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 5.3.

Dose delays and modifications will be made as indicated in the following tables. The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.0).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until 30 days after removal from study or death, whichever occurs first. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

5.3 Monitoring and Toxicity Management

Table 5.3 Palbociclib Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment.

Toxicity	Intervention with Palbociclib
Uncomplicated Grade 3 neutropenia *(ANC ≥500 - <1000/mm3)*	• 1st occurrence: Hold drug. If ANC recovers (ANC ≥ 1000) within 2 weeks, resume at same dose. • If ANC takes longer than 2 weeks to recover (ANC≥1000), but within 3 weeks, then resume drug and decrease drug by 1 dose level. • Recurrent uncomplicated Grade 3: Hold drug. If ANC recovers (ANC ≥1000) within 2 weeks, resume drug and decrease drug by 1 dose level.

Grade 3 neutropenia *(ANC<1000/mm3)* **associated with a documented infection or fever ≥38.5**°C	• Hold drug. If ANC recovers (ANC ≥ 1000) within 3 weeks, resume drug and decrease drug by 1 dose level. • If these parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should permanently discontinue palbociclib.
Grade 4 neutropenia (ANC < 500/mm3)	• 1stoccurrence: Hold drug. Resume once ANC ≥1000 and decrease dose by 1 dose level. • Recurrent Grade 4 neutropenia: Hold drug. Resume once ANC ≥1000 and decrease dose by an additional dose level.
Grade 3 or 4 thrombocytopenia (platelet count < 50,000)	• 1st occurrence: Hold drug until platelet level ≥ 100,000, then resume drug and decrease by 1 dose level. • Recurrent Grade 3 thrombocytopenia: hold drug until platelet level ≥100,000, then decrease drug by an additional dose level.
Grade ≥3 non-hematologic toxicity *(including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)*;	• 1st occurrence: Hold drug until toxicity decreases to ≤ Grade 1 or to baseline, then resume drug and decrease by 1dose level. • Recurrent toxicity: Hold drug until toxicity decreases to ≤ Grade 1 or to baseline, then decrease drug by an additional dose level.
Grade 2 non-hematologic toxicity persisting despite optimal medical treatment, deemed unacceptable in the investigator's judgment, and lasting at least 2 weeks;	• 1st occurrence: Hold drug until toxicity decreases to ≤ Grade 1 or to baseline, then resume drug at same dose level. • Recurrent toxicity: Hold drug until toxicity decreases to ≤ Grade 1 or to baseline, then resume drug and decrease by 1 dose level.

QTc prolongation management

In the event of QTc prolongation, possible alternative reversible causes such as serum electrolyte abnormalities, or usage of concomitant medications with the potential to prolong the QTc interval should be evaluated. If such reversible causes are identified, then they should be corrected accordingly (i.e., correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation (if possible) of concomitant medications known to prolong the QT interval. Recommended dose modifications in the event of QTc prolongation are provided in Table 5.3.1.

Table 5.3.1 Palbociclib Dose Modifications in the Event of QTc Prolongation

Toxicity (NCI CTC Grade, Version 4.0)			
	Grade 2 QTc prolongation (>480 and <500 msec, or 60 msec above baseline)	**Grade 3 QTc prolongation** (≥ 501 msec)	**Grade 4 QTc prolongation** (≥ 501 msec or >60 ms change from baseline and lifethreatening signs including Torsades de points)

Reversible Cause identified	Treat reversible cause Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec Continue at the same dose level (1)	Treat reversible cause Withhold treatment until QTc <500 msec Resume treatment at the same dose level. Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue
No reversible cause identified	Consult cardiology and initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec; Continue at the same dose level (1)	Withhold treatment until QTc <500 msec Resume treatment at the next lower dose level (2) Consult cardiology and monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue

1. If the QTc remains above 480 msec for more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the study medical monitor, taking into account the emerging safety data from palbociclib trials and the investigator's best medical judgment.
2. If the Grade 3 QTc prolongation occurs again after one dose reduction, further dose adjustment and/or discontinuation should be discussed with study medical monitor in consultation with a cardiologist, taking into consideration the emerging safety data from palbociclib trials and the investigator's best medical judgment.

5.3.1 Toxicity Management – Palbociclib

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 may need to be adjusted as described in section 5.2. In the event treatment interruption is deemed necessary for either palbociclib or the endocrine therapy, treatment with the other medication will continue as planned.

If the retreatment parameters (see section 5.) are met within 3 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Please refer to Dose Reductions Section for adverse events requiring dose reduction at the time of treatment resumption.

If the retreatment parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should permanently discontinue palbociclib treatment.

Patients holding palbociclib for surgery are allowed to hold 7 days before and up to 3 weeks after surgery, and are allowed to resume palbociclib therapy once satisfactory wound healing and recovery have occurred. Patients should continue endocrine therapy if palbociclib is held for surgery.

Patients discontinuing palbociclib treatment due to treatment-related toxicity will come off study, but should continue on endocrine therapy as per the investigator's discretion.

Reversible Cause identified	Treat reversible cause Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec Continue at the same dose level (1)	Treat reversible cause Withhold treatment until QTc <500 msec Resume treatment at the same dose level. Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue
No reversible cause identified	Consult cardiology and initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec; Continue at the same dose level (1)	Withhold treatment until QTc <500 msec Resume treatment at the next lower dose level (2) Consult cardiology and monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue

1. If the QTc remains above 480 msec for more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the study medical monitor, taking into account the emerging safety data from palbociclib trials and the investigator's best medical judgment.
2. If the Grade 3 QTc prolongation occurs again after one dose reduction, further dose adjustment and/or discontinuation should be discussed with study medical monitor in consultation with a cardiologist, taking into consideration the emerging safety data from palbociclib trials and the investigator's best medical judgment.

5.3.1 Toxicity Management – Palbociclib

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 may need to be adjusted as described in section 5.2. In the event treatment interruption is deemed necessary for either palbociclib or the endocrine therapy, treatment with the other medication will continue as planned.

If the retreatment parameters (see section 5.) are met within 3 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Please refer to Dose Reductions Section for adverse events requiring dose reduction at the time of treatment resumption.

If the retreatment parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should permanently discontinue palbociclib treatment.

Patients holding palbociclib for surgery are allowed to hold 7 days before and up to 3 weeks after surgery, and are allowed to resume palbociclib therapy once satisfactory wound healing and recovery have occurred. Patients should continue endocrine therapy if palbociclib is held for surgery.

Patients discontinuing palbociclib treatment due to treatment-related toxicity will come off study, but should continue on endocrine therapy as per the investigator's discretion.

5.3.2 Toxicity Management – Endocrine Therapy

No dose reduction for endocrine therapy is permitted, but dosing interruptions are allowed. Treatment interruptions for up to 3 cumulative weeks for endocrine therapy –related toxicities or personal reasons are allowed as per the investigator's best medical judgment.

Patients discontinuing endocrine therapy due to treatment-related toxicity will be discontinued from protocol therapy and come off study. Further endocrine therapy is encouraged and is at the discretion of the treating physician.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Table 6.1.

Screening scans and EKGs must be completed within 28 days prior and all labs within 14 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All **on-study** visit procedures (i.e.,scans) are allowed a window of ± 5 days unless otherwise noted. All labs are allowed a window of ± 3 days. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

Patients are allowed a +/- one week window as needed for travel, holidays, and weather for each monthly fulvestrant injection. Patients are allowed a +/-3day window for the C1D15 loading dose.

Up to a two week break in tamoxifen is allowed if required for a minor surgical procedure.

Up to a 2 week delay in start of palbociclib is allowed for any reason. Each cycle will start with the first dose of administered palbociclib, so if a cycle is delayed by one week, day one of that cycle will be the first day of palbociclib. No change will be made in the dosing schedule of fulvestrant or tamoxifen.

Radiation to a single site of disease for palliation of pain or stereotactic radiation for brain metastases is allowable IF other sites of disease are able to be followed for assessment of response to treatment; radiation for any other reason requires prior approval from the Protocol Chair.

Palbociclib may be held up to two weeks for radiation, but hormonal treatment should continue. A longer duration hold may be permissible in case of delayed recovery from radiation, but must be approved by the overall study PI. Palbociclib may be re-started once labs are within treatment parameters.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in a password protected electronic database that meets HIPAA requirements.

6.2 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to:

- Disease progression
- The occurrence of an adverse event or a concurrent illness
- A patient's request to end participation
- A patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent.
- There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

Table 6.1 Schedule of Study Procedures and Assessments

Procedure	Baseline [1]	Cycle 1 Day 1	Cycle 1 Day 15-21	Every 4 weeks	Every 8 weeks	Off Study
CLINICAL ASSESSMENTS:						
Physical Exam	X			X		(X)
Vital Signs, Height	X[2]			X		
Performance Status	X			X		
LABORATORY TESTS:						
Hematology (CBC with diff, platelets)	X[#]	X[#]		X[**]		X
Chemistries [3]	X[#]	X[#]		X		X
PT/INR, PTT	X					
Electrocardiogram (ECG)	X				X	(X)
Pregnancy Test [4]	X[*]					
IMAGING:						
CT or MRI[8]	X				X[8]	X
Bone scan	X				X[8] (optional)	X
TREATMENT: [5]						
Fulvestrant (choose one hormone therapy)		q28days, with an additional loading dose on C1D15 only				
Tamoxifen (choose one hormone therapy)		20 mg PO daily				
Palbociclib		100 or 125 mg PO daily day 1-21 q 28 days				
CORRELATIVE BLOOD/TISSUE STUDIES: [6]						
Whole Blood for ptDNA	X[6f]					
Archival tumor sample	X[6e]					
Tumor biopsy/sample	X[6d]		X[6d]			(X[6c])
Skin biopsy	X[6a]		X[6a]			
OTHER ASSESSMENTS:						
Concomitant Medication Review	X			X		X
Symptom/Toxicity Assessment	X			X		X[7]

[#] Required ≤ 14 days prior to first treatment (i.e., day 1); baseline labs may be used if within window.
[*] Required ≤ 7 days prior to first treatment (i.e., day 1) unless otherwise noted.
[**] Required ≤ 3 days prior to each specified treatment (exceptions may be made to extend this window, with approval by the Protocol Chair/designee).

Patients are allowed a +/- one week window as needed for travel, holidays, and weather for each monthly fulvestrant injection. Patients are allowed a +/-3day window for the C1D15 loading dose.

(X) = Optional assessment.

1. Baseline assessments are required within 28 days of first treatment (i.e., day 1), unless otherwise noted.
2. Height at baseline only.
3. Chemistries to include measurement of sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, calcium, total protein, albumin, AST, ALT, and alkaline phosphatase.
4. Pregnancy test (serum or urine) is required for women of childbearing potential.
5. Treatment will consist of fulvestrant or tamoxifen given with palbociclib. The choice of hormone therapy is at the discretion of the treating physician. Palbociclib will be given at either 100 mg or 125 mg daily by mouth for 21 days, every 28 days. Patients will be allocated to a specific dose: at the time of progression, patients taking 100 mg from the start of study therapy will have the option to increase their dose to 125 mg and continue therapy depending on response.
6. Correlative blood/tissue studies (refer to the Study Procedures Manual for collection, labeling, processing and shipping instructions):
   a. A 3mm skin punch biopsy will be obtained at baseline and on day 14-21 of cycle 1 to assess for inhibition of RB phosphorylation for all patients enrolled on the trial.
   b. A 18 gauge core needle biopsy or FNA (with tissue block) will be obtained at baseline and on day 14-21 of cycle 1 to assess for inhibition of RB phosphorylation for patients with accessible tumor enrolled on the trial. For skin tumor biopsies, at least two 3mm or one 5mm punch biopsy should be obtained.
   c. An optional tumor biopsy is requested at the time of progression to evaluate markers of resistance to CDK inhibition.
   d. Biopsies are required, however patients with lung disease or inaccessible sites of disease will be allowed to enroll on the trial without a tumor biopsy at the discretion of the principal investigator
   e. Archival primary tumor tissue should be submitted for all patients if available
   f. Two 10 cc Streck tubes will be collected for ptDNA analysis before start of study therapy, during screening or on Cycle1 Day1.
7. All subjects must have a final toxicity assessment at least 30 days following the last dose of study
8. Imaging frequency may be extended to every 12 weeks for patients with stable or responding disease on the scan following cycle 12. Patients with uncertain disease status or significant visceral organ involvement should continue with imaging every 8 weeks.

6.3 Usage of Concurrent/Concomitant Medications

All prior treatment or medication administered during the 30 days preceding the first dose of study treatment and any concomitant therapy administered to the subject throughout the study until 30 days after the final dose of study treatment must be recorded on the Prior and Concomitant Therapy page of the electronic case report form (eCRF). The generic name of the drug (or trade name for combination drugs) must be specified along with the duration of treatment and indication for use. If concomitant medication/therapy is administered for an adverse event (AE), investigators will record that AE on the AE page of the eCRF.

Supportive care medications are allowed at any time on trial. Specifically, the following agents are permitted:

- Antiemetics
- Antidiarrheal therapy
- Antiallergic measures such as corticosteroids and antihistamines
- Bisphosphonates: Subjects being treated with bisphosphonates when they enter the study may continue the medication as long as the dose is stable. Subjects may also initiate bisphosphonate therapy while on protocol therapy if it is thought to be medically necessary.
- Agents to assist in management of endocrine therapy-induced side effects (NSAIDs, gabapentin, duloxetine, venlafaxine, citalopram, etc).

Growth factors, including GCSF, should not be used for upfront prophylaxis, but may be used to treat neutropenia associated with complications, and should follow established ASCO guidelines. Use outside this indication should be discussed with the study PI. Concurrent metformin is allowable. The use of concurrent investigational or other antitumor therapies, other than endocrine therapy, is not permitted.

Missed doses of either endocrine therapy or palbociclib (during a cycle) are not made up.

Strong CYP3A inhibitors/inducers are not allowed on study. Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, Palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans. The concurrent use of CYP3A inhibitors, including amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit, are not allowed in the study. Grapefruit and grapefruit products should be avoided before receiving the first dose of palbociclib.

The concurrent use of CYP3A inducers, including carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, and St. John's Wort, are not allowed in the study. This medication list may also be found in Appendix 5.

Concomitant use of moderate CYP3A inducers and CYP3A substrates is allowable on study, however precaution should be exercised for use of any concomitant medication. If needed, alternative antacid therapies may be used including H2-receptor antagonists and locally acting antacids.

H2-receptor antagonists should be administered with a staggered dosing regimen (twice daily). The dosing of palbociclib should occur at least 10 hours after H2-receptor antagonist evening dose and 2 hours before the H2-receptor antagonist morning dose. Local antacid should be given at least 2 hours before or after palbociclib administration.

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

The use of herbal medicine is not recommended during protocol treatment.

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

Please see Appendix 5 for full list of prohibited drugs.

6.4 Dietary Restrictions

Palbociclib should be taken with food. There are no dietary restrictions for tamoxifen.

Ingestion of grapefruit, grapefruit juice or any product containing grapefruit, are not allowed in patients participating in the study.

7 Adverse Events: List And Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List(s) for Palbociclib

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

In a phase II trial of palbociclib alone for advanced breast cancer, the only toxicities > grade 3 observed were transient neutropenia (50%) and thrombocytopenia (21%).30 In a phase II trial of palbociclib plus letrozole for first-line therapy of hormone receptor positive breast cancer, the most common AEs reported were neutropenia, leukopenia, and fatigue.31,32 The median time to first treatment delay for neutropenia was 58 days, and the median duration of treatment delay until recovery was 5 days (range 1-16 days). In general, hematologic abnormalities were adequately managed with standard supportive care, were not complicated, and resolved during the drug hold with no cumulative toxicity noted.

In the phase I, dose-escalation trial of palbociclib alone in advanced cancers,34 QT interval changes were also evaluated in detail. While 26 of 41 patients had a maximum increase of <30 msec from baseline QTc, zero patients had an on-treatment value exceeding 500 msec.

7.1.2 Adverse Event List(s) for Commercial Agent(s) – Tamoxifen and Fulvestrant

The most common adverse events experienced with use of tamoxifen include hot flashes, night sweats, and vaginal discharge. Venous thromboembolic disease and endometrial cancer are rare risks of tamoxifen.

Commonly reported side effects seen with fulvestrant have been injection site pain, nausea, muscle, joint, and bone pain, headache, tiredness, hot flashes, vomiting, loss of appetite, weakness, cough, constipation, shortness of breath, and increased liver enzymes Fulvestrant has not been studied in patients with severe liver problems.

Package inserts for tamoxifen and fulvestrant can be found at:

- Fulvestrant: http://www.azpicentral.com/faslodex/faslodex.pdf#page=1
- Tamoxifen: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/017970s054lbl.pdf

7.1.3 Antitumor Effect – Solid Tumors

Progression and response in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria PFS is defined as Definitions

Evaluable for PFS

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable).

Patients with evaluable disease only are assessable for stable disease.

7.1.3.1 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by

imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). Bone lesions may be measureable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable. (e.g., PSA, CA-125, CA19-9, CEA)

Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

7.1.3.2 Response Criteria (using RECIST 1.1)

Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD)

At least a 20% increase in the sum of the SLD of target lesions, taking as reference the smallest sum SLD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of one or more new lesions.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 7.1 Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	≥ 4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	≥ 4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥ 4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

Duration of Response

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

Clinical Benefit Rate

Defined as the proportion of patients whose best overall response, according to RECIST, is either complete response (CR), a partial response (PR) or stable disease (SD) lasting for at least 24 weeks.

7.2 Evaluation of Safety

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.03 (v4.03) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;

- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

7.3.2.1 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.2 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.3 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example,

although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or Study Chair, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.3.2.5 Expectedness

Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

7.3.2.6 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

7.4 Recording of an Adverse Event

All treatment related adverse events, and all grade 3 and above adverse events whether or not the event is believed to be associated with use of the study drug will be entered into OnCore®. Data about these events and their severity will be recorded using the NCI CTCAE v4.03.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

7.5 Adverse Events Monitoring

7.5.1 Site Requirements for Reporting SAEs to HCRN

All serious adverse events must be reported to HCRN within 1 business day after the investigator becomes aware of the event. Events should be reported using the HCRN SAE form, found in the Study Procedures Manual (SPM). The report may be sent either electronically [redacted] or faxed [redacted]. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Report and the email correspondence or fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information must also be reported within 1 business day of receipt of the information by the site investigator. Follow-up information should be submitted to HCRN either electronically [redacted] or faxed [redacted]. Follow up events should be reported using the SAE Report Form, stating that this is a follow-up to the previously reported SAE and providing the follow-up number if appropriate. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

When HCRN received an SAE from a site the following process will be followed:

1. HCRN reviews report for completeness and corresponds with site to resolve questions
2. HCRN sends completed SAE to Study Chair (Dr. Rugo) for assessment of relatedness and expectedness within 1 business day
3. Study Chair responds to HCRN within 1 business day
4. If the event is deemed serious, unexpected and reasonably related will be reported as mentioned in last paragraph of section 7.5.1, and sections 7.5.2 and 7.5.3.

HCRN will disseminate information regarding serious adverse events to the participating sites within 5 days of review of the information by the Study Chair (or her designee in the event of extended absence) only in the case that the event(s) is believed to be unexpected and related (i.e., possibly, probably, or definitely) to the study medication. HCRN will be responsible for reporting of events to Pfizer as described below.

7.5.2 HCRN Requirements for Reporting SAEs to Pfizer

HCRN will report related SAEs to Pfizer within **1 business day** of receipt of the SAE Reporting Form. Follow-up information will be provided to Pfizer as reasonably requested.

7.5.3 UCSF HDFCCC Requirements for Reporting SAEs to FDA

UCSF HDFCCC will manage the Investigational New Drug Application (IND) associated with this protocol.

HCRN will send UCSF any SAE that is unexpected and reasonably related (i.e., possible, probably, definite) to the study treatment. UCSF will report these events to the FDA.

According to CFR 312.32, unexpected fatal or life-threatening events possibly related with the use of the study drug (drugs) will be reported to the FDA by fax or by phone as soon as possible, but in no event later than 7 calendar days after the initial receipt of the information regarding the event. The fax should be sent to the FDA project manager assigned to the IND. UCSF will submit a comprehensive written report as an amendment to the IND within an additional 8 days (15 calendar days total).

UCSF will report all other serious unexpected events associated with the use of the study drug to the FDA as an amendment to the IND as soon as possible, but in no event later than 15 calendar days after initial receipt of the information regarding the event.

UCSF will be responsible for all communication with the FDA including but not limited to the initial IND submission, 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, UCSF will submit a copy of these reports to Pfizer at the time of submission to FDA.

7.5.4 IND Safety Reports Unrelated to this Trial

Pfizer will send IND safety reports from external studies that involve palbociclib to HCRN [redacted]. HCRN will forward the safety reports to the Study Chair who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites within 1 business day of receipt. IND safety reports will also be made available to sites participating in this study through the Oncore database.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

7.5.5 HCRN Expedited Reporting to the HDFCCC Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, HCRN must notify the HDFCCC DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

UCSF DSMC:

DSMC Chair:

Alan Venook, MD
[redacted]
UCSF
San Francisco, CA 94115

DSMC Co-Chairs:

Andrew Ko, MD
[redacted]

Thierry Jahan, MD
[redacted]

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

Primary Endpoint

Incidence of grade 3 or 4 neutropenia with 100 mg and 125 mg dosing of palbociclib in combination with either tamoxifen or fulvestrant per CTCAE 4.0

Secondary Endpoints

Progression free survival (PFS), defined as the interval from study entry to the first documented evidence of disease progression by RECIST 1.1. Patients who remain event-free at the time of analysis will be censored at their last date of follow-up.

Objective response (CR+PR) and clinical benefit (CR+PR+SD≥24wk) in patients with measurable disease as assessed by RECIST 1.1.

Toxicity will be reported using CTCAE v4.03.

Laboratory endpoints include paired measurements of inhibition of RB phosphorylation in tumor and in skin at baseline and D14-21 of treatment, and markers obtained from circulating plasma DNA.

8.2 Accrual Rate

Total expected accrual is 70 patients. Up to 5 randomized patients that do not receive study treatment may be replaced during the enrollment period and removed from the primary analysis. The anticipated accrual rate will be 5-8 pts per month. If at least 8 TBCRC sites participate in this trial, at least one patient should be able to be enrolled per month in this trial. Although there is a limit to the number of lines of chemotherapy, this should not impact enrollment significantly.

Assuming a linear increase over the first 6 months to target accrual, approximately 12 to 18 months of patient accession is anticipated. All patients that remain on treatment must be followed for a minimum of four months to inform the primary endpoint of neutropenia.

8.2.1 Sample Size and Power Estimate

Each arm of palbociclib given in combination with endocrine therapy will be evaluated against a null hypothesis of unacceptable rates of Grade 3/4 neutropenia as 63.6% of the treated population which is defined from the PALOMA-1 trial. This corresponds to the upper bound of a 90% confidence interval from the report from Finn et al[10] that 45 (54%) of 83 patients (90% CI: 44.6% to 63.6%) experienced the AE. A single-stage Binomial exact test will be conducted in each arm using a maximum one-sided Type I alpha at 0.05 for each test. With 35 patients treated at each dose level, there is 78% power to reject the null if the true rate is 43.6% (Δ = 20.0%).

8.3 Analyses Plans

The primary analysis of the rate of Grade 3/4 neutropenia will reject the null hypothesis if 17 or fewer of 35 patients (<49%) experience the AE (exact alpha = 0.049). The observed rate in each arm will be reported with two-sided 90% exact confidence intervals.

The evaluation of PFS will be conducted separately by cohort, with the survival function estimated using Kaplan-Meier method and 90% confidence bands will be computed using Greenwoods' formula. For secondary endpoints of objective response and clinical benefit the proportion observed in each arm will be reported with 90% exact Binomial confidence intervals.

Descriptive statistics will be used to summarize expression of total Rb, phospho-Rb, Ki-67 and TUNEL staining at baseline and D14-21 of treatment with each Arm. Absolute change from baseline will be calculated and assessed for statistical significance within arm using the paired Student's t-test. If Gaussian assumptions are observed qualitatively to fail to hold, a Wilcoxon signed rank test will be used for inference. Based on limited historical data to define equivalence, differential inhibition of phospho-RB with 100 and 125 mg palbociclib will be explored in general linear model with baseline measurements as an independent covariate (two-sample t-test). Changes from baseline will be reported with 95% confidence intervals. Correlation in baseline measures in skin and tumor and changes from baseline will be summarized using Pearson coefficients

The association of measures of inhibition of phospho-RB in skin and tumor with PFS will be exploratory and hypothesis generating, and use the Cox model for point and interval estimates. Changes in these parameters will be assessed as continuous factors using C-index and explored under varying partitions of the correlative endpoints using the method of LeBlanc and Crowley (1992). This work will be done at Dana Farber Cancer Center (Scott Rodig and Geoff Shapiro)

Plasma will be evaluated for circulating plasma DNA [redacted] at Johns Hopkins University, with technology/procedures to be decided at the end of the study. This is an exploratory endpoint.

8.4 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.03 and the frequency of toxicity overall and by term will be tabulated by grade and by attribution to treatment.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, each site Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until the FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed.

Each site investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The local IRBs must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by each site's local Institutional Review Board. The initial protocol and all protocol amendments must be approved by each site's local IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the site IRB -approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the local IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by the local IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the site investigator must then notify HCRN within 1 business day and the site IRB according to local guidelines. The Study Chair and HCRN will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

Each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included.

The Study Chair shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Study Chair will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The site Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Site personnel will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents.

In accordance with federal regulations, the site investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

9.7 Oversight and Monitoring Plan

Oversight:
The study will be conducted in accordance with the UCSF Helen Diller Family Comprehensive Cancer Center's Data and Safety Monitoring Plan (DSMP) and Data and Safety Monitoring Committee. See Appendix 2: Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional details.

In addition HCRN oversight activities include:

- Review of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress and safety information to the Study Chair as required
- Notify participating sites of adverse events requiring expedited reporting and of subsequent DSMC recommendations for study modifications

HCRN will compile data summary reports for this trial and submit these reports monthly to the Study Chair. HCRN will submit data summary reports at a minimum of twice a year to the HDFCCC DSMC for review.

Monitoring:
Study monitoring will include a risk-based monitoring strategy for cause as defined in the HCRN Data Management Plan associated with this protocol. Routine CRF monitoring will be in-house at HCRN.

On site monitoring visits to the trial sites may be made periodically during the trial, to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The site investigator and institution guarantee access to source documents by HCRN or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by Pfizer or its designee as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

9.8 Record Keeping and Record Retention

The site Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The site Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records, such as progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Study Chair correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the site investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

9.9 Specimen Banking

Any leftover study tissue or blood samples may be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. The study PI and collaborators have approval by the TBCRC, which has custodial oversight of all biospecimens collected as part of a TBCRC trial, to address the research questions described in

the protocol document. All future use as part of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the TBCRC according to its established policies, whether the specimens are stored in a central site or at a local institution or in a virtual repository.

9.10 Publications

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to the TBCRC Central Office and all participating sites prior to submission for publication or presentation.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

Appendices

Appendix 1 Performance Status Criteria[I]

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

[I] – Eastern Cooperative Oncology Group Performance Status available at: http://www.ecog.org/general/perf_stat.html

Appendix 2 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study include:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly Site Committee meetings. These discussions are documented in the Site Committee meeting minutes. The discussion will include the number of subjects, significant toxicities in accordance with the protocol, and observed responses.

All institutional Phase 2 or 3 studies are designated with a moderate risk assessment. The data is monitored twice per year with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

Adverse Event Review and Monitoring

All grade(s) 3-5 adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, HCRN's Clinical Trial Management System.

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the HDFCCC Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

If a death related either to the investigational drug or any research related procedure occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s), the participating site(s) must notify HCRN within 1 business day and HCRN must then notify the HDFCCC DSMC Chair or qualified alternate within 1 business day of knowledge of this event. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If the Study Chair observes an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), a report should be submitted to the HDFCCC DSMC by HCRN at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, HCRN must notify the HDFCCC DSMC Chair, the DSMC Manager, and all participating sites within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days.

Participating sites must notify their IRBs according to local guidelines.. **Data and Safety Monitoring Committee Contacts**

DSMC Chair:	DSMC Monitors:
[redacted] UCSF San Francisco, CA 94158	[redacted] UCSF Helen Diller Family Comprehensive Cancer Center San Francisco, CA 94143

* DSMP approved by NCI 09/February2012

Appendix 3 UCSF Policy/Procedure for Required Regulatory Documents for UCSF Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Study Chair holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- IRB approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Institutional Review Board (IRB) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to IRB with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Study Chair 's signature
- For the Study Chair and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to IRB and HCRN.
- MedWatch reporting to FDA and funder (Pfizer)
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

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Appendix 4 Multicenter Institutional Studies

4.1 Data and Safety Monitoring Plan for Multicenter Study (Phase 2 or 3 Institutional Study)

Multi-Center Guidelines

Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Hoosier Cancer Research Network (HCRN). The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. HCRN will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to HCRN.

Records Retention

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. HCRN will inform the investigator at each site at such time that the records may be destroyed.

Multicenter communication

HCRN provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The HCRN will also coordinate, at minimum, quarterly conference calls with the participating sites or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse Events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol Violations
- Other issues affecting the conduct of the study

Adverse event reporting to the DSMC will include data from all participating sites. HCRN will be responsible for monitoring data at each of the participating sites.

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Appendix 5 Prohibited Medications (to be reviewed by Pharmacist)

Drug	Trade Name
Amprenavir	Agenerase
Atazanavir	Reyataz
Boceprevir	Victrelis
Bosentan	Tracleer
Carbamazepine	Carbatrol, Epitol, Equetro, TEGretol, TEGretol XR
Clarithromycin	Biaxin, Biaxin XL, Biaxin XL-Pak
Conivaptan	Vaprisol
Debrafenib	Tafinlar
Delavirdine	Rescriptor
Efavirenz	Sustiva
Etravirine	Intelence
Fosamprenavir	Lexiva, Telzir
Grapefruit, grapefruit juice or any product containing grapefruit	
Gingko Biloba and Ginseng	
Indinavir	Crixivan
Itraconazole	Sporanox
Ketoconazole	Nizoral
Lopinavir	(+ritinovir)=Kaletra
Nefarelin	Synarel
Nefazodone	Serzone
Nelfinavir	Viracept
Nevirapine	Viramune
Phenobarbital	Solfoton, Luminal
Phenytoin	Dilantin
Primidone	Mysoline
Posaconazole	Noxafil
Rifabutin	Mycobutin
Rifampin	Rifadin
Rifapentine	Priftin
Ritonavir	Isentress
Saquinavir	Invirase
Seville (sour) oranges, starfruit	
St. John's Wort	
Telaprevir	Incivek
Telithromycin	Ketek
Verapamil	Calan, Calan SR, Isoptin SR, Verelan, Verelan PM, Isoptin, Isoptin I.V., Covera-HS
Voriconazole	Vfend

Note: Please consult with your pharmacist about all concomitant medications to ensure they are not strong CYP3A4 inducers/inhibitors. Caution should be used in combination with moderate CYP3A4 inducers/inhibitors.

References:

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5.3.2 Toxicity Management – Endocrine Therapy

No dose reduction for endocrine therapy is permitted, but dosing interruptions are allowed. Treatment interruptions for up to 3 cumulative weeks for endocrine therapy –related toxicities or personal reasons are allowed as per the investigator's best medical judgment.

Patients discontinuing endocrine therapy due to treatment-related toxicity will be discontinued from protocol therapy and come off study. Further endocrine therapy is encouraged and is at the discretion of the treating physician.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Table 6.1.

Screening scans and EKGs must be completed within 28 days prior and all labs within 14 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All **on-study** visit procedures (i.e.,scans) are allowed a window of ± 5 days unless otherwise noted. All labs are allowed a window of ± 3 days. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

Patients are allowed a +/- one week window as needed for travel, holidays, and weather for each monthly fulvestrant injection. Patients are allowed a +/-3day window for the C1D15 loading dose.

Up to a two week break in tamoxifen is allowed if required for a minor surgical procedure.

Up to a 2 week delay in start of palbociclib is allowed for any reason. Each cycle will start with the first dose of administered palbociclib, so if a cycle is delayed by one week, day one of that cycle will be the first day of palbociclib. No change will be made in the dosing schedule of fulvestrant or tamoxifen.

Radiation to a single site of disease for palliation of pain or stereotactic radiation for brain metastases is allowable IF other sites of disease are able to be followed for assessment of response to treatment; radiation for any other reason requires prior approval from the Protocol Chair.

Palbociclib may be held up to two weeks for radiation, but hormonal treatment should continue. A longer duration hold may be permissible in case of delayed recovery from radiation, but must be approved by the overall study PI. Palbociclib may be re-started once labs are within treatment parameters.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in a password protected electronic database that meets HIPAA requirements.

6.2 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to:

6.4 Dietary Restrictions

Palbociclib should be taken with food. There are no dietary restrictions for tamoxifen.

Ingestion of grapefruit, grapefruit juice or any product containing grapefruit, are not allowed in patients participating in the study.

7 Adverse Events: List And Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List(s) for Palbociclib

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

In a phase II trial of palbociclib alone for advanced breast cancer, the only toxicities > grade 3 observed were transient neutropenia (50%) and thrombocytopenia (21%).30 In a phase II trial of palbociclib plus letrozole for first-line therapy of hormone receptor positive breast cancer, the most common AEs reported were neutropenia, leukopenia, and fatigue.31,32 The median time to first treatment delay for neutropenia was 58 days, and the median duration of treatment delay until recovery was 5 days (range 1-16 days). In general, hematologic abnormalities were adequately managed with standard supportive care, were not complicated, and resolved during the drug hold with no cumulative toxicity noted.

In the phase I, dose-escalation trial of palbociclib alone in advanced cancers,34 QT interval changes were also evaluated in detail. While 26 of 41 patients had a maximum increase of <30 msec from baseline QTc, zero patients had an on-treatment value exceeding 500 msec.

7.1.2 Adverse Event List(s) for Commercial Agent(s) – Tamoxifen and Fulvestrant

The most common adverse events experienced with use of tamoxifen include hot flashes, night sweats, and vaginal discharge. Venous thromboembolic disease and endometrial cancer are rare risks of tamoxifen.

Commonly reported side effects seen with fulvestrant have been injection site pain, nausea, muscle, joint, and bone pain, headache, tiredness, hot flashes, vomiting, loss of appetite, weakness, cough, constipation, shortness of breath, and increased liver enzymes Fulvestrant has not been studied in patients with severe liver problems.

Package inserts for tamoxifen and fulvestrant can be found at:

- Fulvestrant: http://www.azpicentral.com/faslodex/faslodex.pdf#page=1
- Tamoxifen: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/017970s054lbl.pdf

7.1.3 Antitumor Effect – Solid Tumors

Progression and response in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria PFS is defined as Definitions

Evaluable for PFS

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable).

Patients with evaluable disease only are assessable for stable disease.

7.1.3.1 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

Clinical Benefit Rate

Defined as the proportion of patients whose best overall response, according to RECIST, is either complete response (CR), a partial response (PR) or stable disease (SD) lasting for at least 24 weeks.

7.2 Evaluation of Safety

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.03 (v4.03) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

7.5 Adverse Events Monitoring

7.5.1 Site Requirements for Reporting SAEs to HCRN

All serious adverse events must be reported to HCRN within 1 business day after the investigator becomes aware of the event. Events should be reported using the HCRN SAE form, found in the Study Procedures Manual (SPM). The report may be sent either electronically [redacted] or faxed [redacted]. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Report and the email correspondence or fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information must also be reported within 1 business day of receipt of the information by the site investigator. Follow-up information should be submitted to HCRN either electronically [redacted] or faxed [redacted]. Follow up events should be reported using the SAE Report Form, stating that this is a follow-up to the previously reported SAE and providing the follow-up number if appropriate. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

When HCRN received an SAE from a site the following process will be followed:

1. HCRN reviews report for completeness and corresponds with site to resolve questions
2. HCRN sends completed SAE to Study Chair (Dr. Rugo) for assessment of relatedness and expectedness within 1 business day
3. Study Chair responds to HCRN within 1 business day
4. If the event is deemed serious, unexpected and reasonably related will be reported as mentioned in last paragraph of section 7.5.1, and sections 7.5.2 and 7.5.3.

HCRN will disseminate information regarding serious adverse events to the participating sites within 5 days of review of the information by the Study Chair (or her designee in the event of extended absence) only in the case that the event(s) is believed to be unexpected and related (i.e., possibly, probably, or definitely) to the study medication. HCRN will be responsible for reporting of events to Pfizer as described below.

7.5.2 HCRN Requirements for Reporting SAEs to Pfizer

HCRN will report related SAEs to Pfizer within **1 business day** of receipt of the SAE Reporting Form. Follow-up information will be provided to Pfizer as reasonably requested.

7.5.3 UCSF HDFCCC Requirements for Reporting SAEs to FDA

UCSF HDFCCC will manage the Investigational New Drug Application (IND) associated with this protocol.

HCRN will send UCSF any SAE that is unexpected and reasonably related (i.e., possible, probably, definite) to the study treatment. UCSF will report these events to the FDA.

According to CFR 312.32, unexpected fatal or life-threatening events possibly related with the use of the study drug (drugs) will be reported to the FDA by fax or by phone as soon as possible, but in no event later than 7 calendar days after the initial receipt of the information regarding the event. The fax should be sent to the FDA project manager assigned to the IND. UCSF will submit a comprehensive written report as an amendment to the IND within an additional 8 days (15 calendar days total).

UCSF will report all other serious unexpected events associated with the use of the study drug to the FDA as an amendment to the IND as soon as possible, but in no event later than 15 calendar days after initial receipt of the information regarding the event.

UCSF will be responsible for all communication with the FDA including but not limited to the initial IND submission, 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, UCSF will submit a copy of these reports to Pfizer at the time of submission to FDA.

7.5.4 IND Safety Reports Unrelated to this Trial

Pfizer will send IND safety reports from external studies that involve palbociclib to HCRN [redacted]. HCRN will forward the safety reports to the Study Chair who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites within 1 business day of receipt. IND safety reports will also be made available to sites participating in this study through the Oncore database.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

7.5.5 HCRN Expedited Reporting to the HDFCCC Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, HCRN must notify the HDFCCC DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

UCSF DSMC:

DSMC Chair:

Alan Venook, MD
[redacted]
UCSF
San Francisco, CA 94115

DSMC Co-Chairs:

Andrew Ko, MD
[redacted]

Thierry Jahan, MD
[redacted]

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

Primary Endpoint

Incidence of grade 3 or 4 neutropenia with 100 mg and 125 mg dosing of palbociclib in combination with either tamoxifen or fulvestrant per CTCAE 4.0

Secondary Endpoints

Progression free survival (PFS), defined as the interval from study entry to the first documented evidence of disease progression by RECIST 1.1. Patients who remain event-free at the time of analysis will be censored at their last date of follow-up.

Objective response (CR+PR) and clinical benefit (CR+PR+SD≥24wk) in patients with measurable disease as assessed by RECIST 1.1.

Toxicity will be reported using CTCAE v4.03.

Laboratory endpoints include paired measurements of inhibition of RB phosphorylation in tumor and in skin at baseline and D14-21 of treatment, and markers obtained from circulating plasma DNA.

8.2 Accrual Rate

Total expected accrual is 70 patients. Up to 5 randomized patients that do not receive study treatment may be replaced during the enrollment period and removed from the primary analysis. The anticipated accrual rate will be 5-8 pts per month. If at least 8 TBCRC sites participate in this trial, at least one patient should be able to be enrolled per month in this trial. Although there is a limit to the number of lines of chemotherapy, this should not impact enrollment significantly.

Assuming a linear increase over the first 6 months to target accrual, approximately 12 to 18 months of patient accession is anticipated. All patients that remain on treatment must be followed for a minimum of four months to inform the primary endpoint of neutropenia.

8.2.1 Sample Size and Power Estimate

Each arm of palbociclib given in combination with endocrine therapy will be evaluated against a null hypothesis of unacceptable rates of Grade 3/4 neutropenia as 63.6% of the treated population which is defined from the PALOMA-1 trial. This corresponds to the upper bound of a 90% confidence interval from the report from Finn et al[10] that 45 (54%) of 83 patients (90% CI: 44.6% to 63.6%) experienced the AE. A single-stage Binomial exact test will be conducted in each arm using a maximum one-sided Type I alpha at 0.05 for each test. With 35 patients treated at each dose level, there is 78% power to reject the null if the true rate is 43.6% (Δ = 20.0%).

8.3 Analyses Plans

The primary analysis of the rate of Grade 3/4 neutropenia will reject the null hypothesis if 17 or fewer of 35 patients (<49%) experience the AE (exact alpha = 0.049). The observed rate in each arm will be reported with two-sided 90% exact confidence intervals.

The evaluation of PFS will be conducted separately by cohort, with the survival function estimated using Kaplan-Meier method and 90% confidence bands will be computed using Greenwoods' formula. For secondary endpoints of objective response and clinical benefit the proportion observed in each arm will be reported with 90% exact Binomial confidence intervals.

Descriptive statistics will be used to summarize expression of total Rb, phospho-Rb, Ki-67 and TUNEL staining at baseline and D14-21 of treatment with each Arm. Absolute change from baseline will be calculated and assessed for statistical significance within arm using the paired Student's t-test. If Gaussian assumptions are observed qualitatively to fail to hold, a Wilcoxon signed rank test will be used for inference. Based on limited historical data to define equivalence, differential inhibition of phospho-RB with 100 and 125 mg palbociclib will be explored in general linear model with baseline measurements as an independent covariate (two-sample t-test). Changes from baseline will be reported with 95% confidence intervals. Correlation in baseline measures in skin and tumor and changes from baseline will be summarized using Pearson coefficients

The association of measures of inhibition of phospho-RB in skin and tumor with PFS will be exploratory and hypothesis generating, and use the Cox model for point and interval estimates. Changes in these parameters will be assessed as continuous factors using C-index and explored under varying partitions of the correlative endpoints using the method of LeBlanc and Crowley (1992). This work will be done at Dana Farber Cancer Center (Scott Rodig and Geoff Shapiro)

Plasma will be evaluated for circulating plasma DNA [redacted] at Johns Hopkins University, with technology/procedures to be decided at the end of the study. This is an exploratory endpoint.