Title: A Phase Ib/II Study of Palbociclib in Combination with Bazedoxifene in Hormone Receptor Positive Breast Cancer

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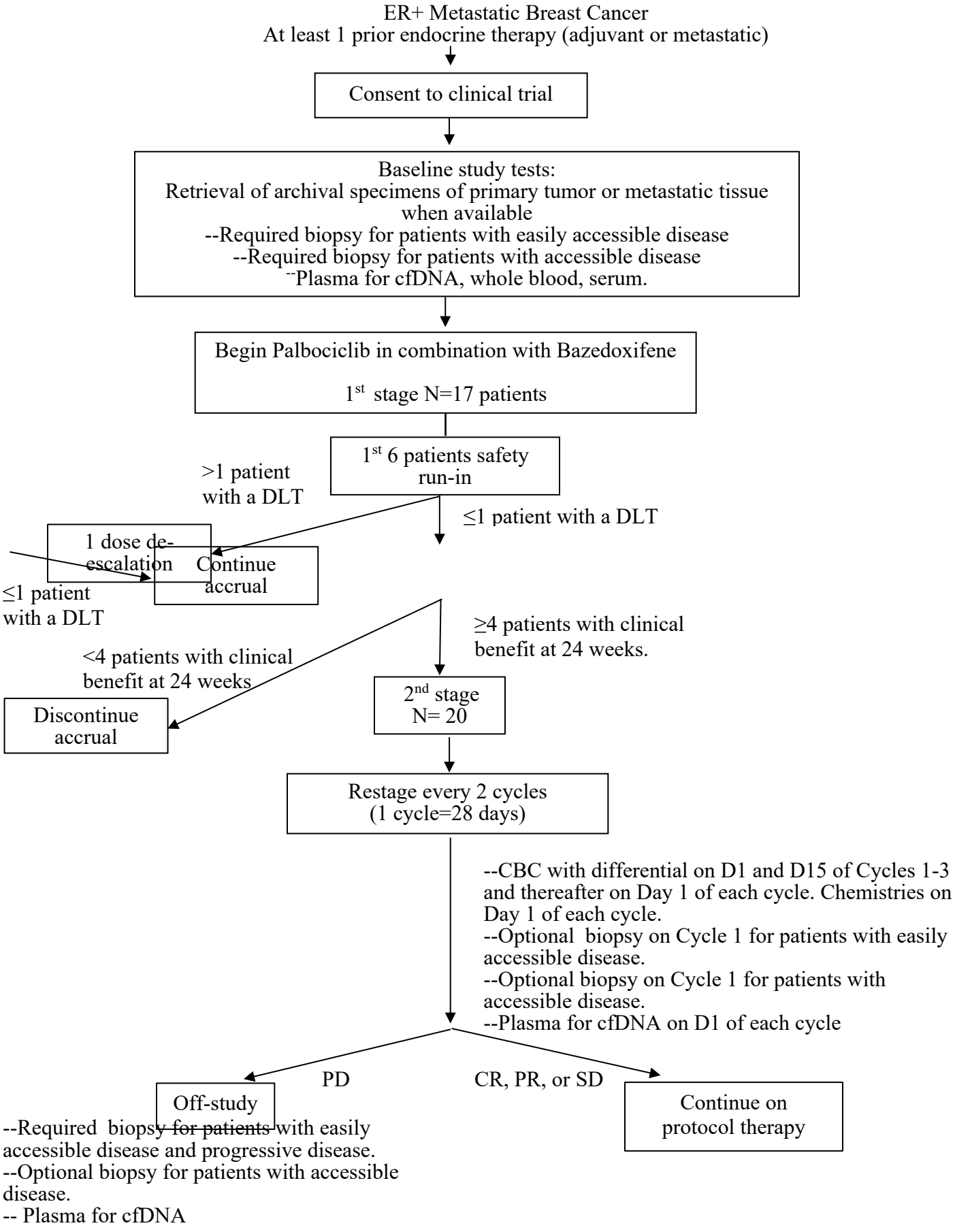
SCHEMA


ER+ Metastatic Breast Cancer
At least 1 prior endocrine therapy (adjuvant or metastatic)
Consent to clinical trial
Baseline study tests:
Retrieval of archival specimens of primary tumor or metastatic tissue when available
--Required biopsy for patients with easily accessible disease
--Required biopsy for patients with accessible disease
--Plasma for cfDNA, whole blood, serum.
Begin Palbociclib in combination with Bazedoxifene
1st stage N=17 patients
1st 6 patients safety run-in
>1 patient with a DLT
≤1 patient with a DLT
1 dose de-escalation
Continue accrual
≤1 patient with a DLT
≥4 patients with clinical benefit at 24 weeks.
<4 patients with clinical benefit at 24 weeks
Discontinue accrual
2nd stage N= 20
Restage every 2 cycles (1 cycle=28 days)
--CBC with differential on D1 and D15 of Cycles 1-3 and thereafter on Day 1 of each cycle. Chemistries on Day 1 of each cycle.
--Optional biopsy on Cycle 1 for patients with easily accessible disease.
--Optional biopsy on Cycle 1 for patients with accessible disease.
--Plasma for cfDNA on D1 of each cycle
PD
CR, PR, or SD
Off-study
Continue on protocol therapy
--Required biopsy for patients with easily accessible disease and progressive disease.
--Optional biopsy for patients with accessible disease.
-- Plasma for cfDNA

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1. OBJECTIVES

1.1 Study Design

This is a non-randomized, open-label, phase Ib/II study designed to evaluate the safety and efficacy of palbociclib, an oral selective CDK 4/6 inhibitor in combination with bazedoxifene, a third generation selective estrogen receptor modulator (SERM) in patients with metastatic hormone receptor positive breast cancer. Patients must have hormone receptor positive (HR+) disease and HER2 negative disease (defined as ER ≥10% or PR≥10%, and HER2- negative by IHC and/or FISH). Patients must have received at least 1 prior endocrine treatment regimen in the advanced setting or have relapsed less than 12 months from completion of adjuvant endocrine treatment. Patients will be re-staged every 2 cycles and will remain on study until there is evidence of progressive disease, unacceptable toxicity, or withdrawal of consent. A safety run-in will be performed after the accrual of the first 6 patients. No more than 1 of 6 patients is to have a dose limiting toxicity before continuing accrual. If more than 1 patient has a dose limiting toxicity, an additional 6 patients will be accrued for a dose de-escalation safety run-in. If more than 1 of 6 patients has a dose limiting toxicity in the dose de-escalation safety run-in, accrual to the study will be discontinued. In the first stage of the two-stage design, 17 patients will be enrolled. If at 24 weeks there are at least 4 patients with clinical benefit accrual will continue to the second stage where up to 20 additional patients will be enrolled. If at least 11 of these 37 patients have clinical benefit, the regimen will be considered worthy of further study.

1.2 Primary Objectives

- To evaluate the clinical benefit rate (CR + PR + SD ≥ 24 weeks) of palbociclib and bazedoxifene in advanced HR+ /HER2- breast cancer.

1.3 Secondary Objectives

- To determine the safety and toxicity profile
- To determine the objective response rate in patients receiving palbociclib and bazedoxifene.
- To determine the progression-free survival of patients receiving palbociclib and bazedoxifene.
- To determine the overall survival of patients receiving palbociclib and bazedoxifene.
- To assess the objective response, clinical benefit rate, progression free survival and overall survival for patients with *ESR1* mutations.

1.4 Correlative Objectives

The correlative studies proposed in this protocol are exploratory and hypothesis-generating. Promising hypotheses may be further explored and/or validated in future studies.

- To explore whether high levels of cyclin D1or phosphorylated Rb are associated with objective response
- Validate the mechanism of action of palbociclib and bazedoxifene by looking at phosphorylated Rb levels, ER levels and ER target gene levels at cycle 1.
- To explore if there is an association between specific genetic alterations and objective response or overall survival by performing Next Generation Sequencing (NGS) in archival metastatic tumor samples and /or prospectively collected metastatic samples.
- Study mechanisms of resistance by studying expression levels of ER, Cyclin D1, phosphorylated Rb and the CDK inhibitors p21, p27 and p16, EGFR, and phosphorylated AKT and by performing NGS of tumors attained after the development of resistance.
- To explore the sensitivity of plasma cell free DNA (cfDNA) and droplet digital PCR (ddPCR) to detect

mutations in metastatic breast cancer.
- To analyze if changes in levels of mutations as determined by plasma cfDNA and ddPCR correlate with response or resistance to treatment.
- Objective response, Clinical benefit rate, Progression free survival and Overall survival in patients with *ESR1* mutations.

In addition to the above studies, specimens will be collected and archived for future studies.
- To collect primary and metastatic samples for future studies
- To collect plasma at baseline and time of progression for future studies

2. BACKGROUND

2.1 Study Disease(s)

The majority of breast cancer mortality is due to hormone receptor positive (HR+) disease [1]. Endocrine treatments are the mainstay therapy for ER+ breast cancer. These treatments include targeting the ER for inhibition using the antagonist tamoxifen, reducing ER activation by suppressing endogenous estrogen production by using aromatase inhibitors (AI) and more recently down regulating and enhancing ER degradation by selective ER degraders (SERDs). Despite effective endocrine treatments, de-novo and acquired endocrine resistance remains an important clinical challenge. This underscores the need for new therapeutic strategies to treat HR+ metastatic breast cancer.

2.2 IND Agents

2.2.1 Palbociclib

PD-0332991 (palbociclib), an orally active pyridopyrimidine, is a potent first-in-class, highly selective reversible inhibitor of CDK4 and CDK6 (IC50 = 11 nM; Ki = 2 nM) with a molecular weight of 447.53. Data from nonclinical studies indicate that palbociclib may have cytoreductive as well as cytostatic effects on tumor cells. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials. CDK4 and CDK6 control G1 to S phase transit by binding to D-type cyclins [2-4]. The CDK4/6/Cyclin D1 complex phosphorylates the retinoblastoma susceptibility (*RB1*) gene product (Rb), releasing the E2F and DP transcription factors that drive expression of genes required for S-phase entry. CDK activity and G1 progression is negatively regulated by Cip-Kip (P27,P21) and INK4 family, typified by p16 [5-9]. Overexpression of p16 in cells with normal Rb inhibits both CDK4-and CDK6- associated kinase activity and Rb phosphorylation, with subsequent cell cycle arrest [10, 11].

There is a strong link between the actions of estradiol and the G1-S phase transition, where the estradiol effector is the cyclin D1-CDK4/6-Rb complex [12]. Cyclin D1 is a direct transcriptional target of ER [13, 14] and microinjection of antibodies to cyclin D1 inhibits estrogen-induced S-phase entry. In addition, anti-estrogen-induced growth arrest of ER+ breast cancer cells is accompanied by decreased cyclin D1 expression [15], while endocrine resistance is associated with persistent cyclin D1 expression and Rb phosphorylation [16]. Consistent with the notion that the main function of cyclin D1 is to activate CDK4/6, its oncogenic activity is dependent on CDK4/6-associated kinase activity [17] and CDK4/6 inhibitors are most effective in tumors with gene amplification and overexpression of cyclin D1 [18-20], which is common in ER+ breast cancer. Genetic aberrations leading to hyperactivation of cyclin D1-CDK4/6 is particularly common in ER+ breast cancer [21], consistent with its critical role in the tumorigenesis of this cancer subtype, making CDK4/6 inhibitors particularly attractive agents for ER+ breast cancer.

Palbociclib Preclinical Data

Palbociclib preclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytoreductive activity. Single agent palbociclib has shown antiproliferative effects (selective G_1 arrest) on Rb-positive cancer cells *in vitro* and *in vivo* [19] 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 [19].

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

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

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

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

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

Palbociclib Pharmacokinetic (PK) Data

To date, pharmacokinetic data have been collected in 8 clinical studies for a total of over 250 advanced cancer

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

The effect of food on the bioavailability of palbociclib when administered as the commercial free base capsule, was investigated in Study A5481021. The administration of the free base formulation of palbociclib with food (including a high fat or a low fat meal given together with palbociclib, or moderate fat meals given 1 hour before and 2 hours after palbociclib) resulted in more uniform drug absorption and significantly reduced the intersubject variability in drug exposure when compared to the administration of free base formulation of palbociclib in a fasted state. The relative bioavailability of the commercial free base capsule administered with food and the isethionate capsule administered under overnight and minimal fasting conditions was investigated in Study A5481036. The two fasting conditions for administration of isethionate capsules represent the 2 extreme scenarios for compliant palbociclib dosing with regard to food intake in the pivotal Phase 1/2 efficacy trial, Study A5481003, in which patients were instructed to fast from 1 hour before until 2 hours after palbociclib dosing. The administration of palbociclib free base capsule formulation with food was found to be bioequivalent to palbociclib isethionate capsule formulation given under both the overnight and minimal fasting conditions. As a result of these findings, it is recommended that free base formulations of palbociclib be administered with food.

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

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

Palbociclib and PF-05089326 caused time-dependent inhibition of CYP3A in in vitro assays. Pharmacokinetic data are available from a midazolam DDI study where the effect of multiple dosing of palbociclib (125 mg QD) on the single-dose PK of a sensitive CYP3A4/5 probe substrate, oral midazolam (2 mg), was evaluated in 26 healthy women of non-childbearing potential (Study A5481012). When midazolam was administered with palbociclib 125 mg QD at steady-state, the mean midazolam plasma C_{max} and AUC_{inf} values increased

approximately 38% and 61%, respectively, as compared with those determined after administration of midazolam alone. These results indicate that palbociclib is a weak time-dependent inhibitor of CYP3A.

Palbociclib Dose Rationale

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

Palbociclib Clinical Data

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

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

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

Two interim analyses for the Phase 2 portion of the study have been conducted. The results of the interim analyses showed consistent trend of clinically meaningful improvements in PFS (primary endpoint). In the first interim analysis (Part 1; N=66), the median PFS for the palbociclib plus letrozole arm was 18.2 months versus 5.7 months for the letrozole alone arm (HR=0.35; 95% CI: 0.17, 0.72; p=0.006). The second interim analysis (N=165) continued to demonstrate a statistically significant improvement in PFS (26.1 vs. 7.5 months, respectively; HR=0.37; 95% CI: 0.21, 0.63; p <0.001) [22]. More recently, the final analysis demonstrated a statistically significant improvement in PFS for the palbociclib plus letrozole arm (20.2 months) versus the letrozole arm (10.2 months) with hazard ratio (HR=0.488; 95% CI: 0.319, 0.748, p=0.0004). These results indicate that the combination of palbociclib with letrozole is well tolerated with a safety profile similar to that seen with either palbociclib or letrozole when administered alone. The most frequently reported treatment-related adverse events included neutropenia, leukopenia, anemia, and fatigue. There were no cases of febrile neutropenia reported to date in this study. Overall, 8 patients in the combination arm were discontinued from the study treatment due to an adverse event, of which 5 were considered treatment-related (grade 3 neutropenia [n=4] and ischemic colitis) and 1 patient from the letrozole alone arm. Additionally, the combination demonstrated antitumor activity, which was consistent with the sensitivity of ER+ breast cancer observed in the preclinical models.

2.2.2 Bazedoxifene

Bazedoxifene is an orally available indole-based selective estrogen receptor modulator (SERM) with two phenyl rings that serve as the core-binding unit. Its structural characteristics differ from those of tamoxifen and raloxifene. Bazedoxifene (20 mg) is approved in the European Union for the treatment of post-menopausal osteoporosis in women at increased risk of fracture. Bazedoxifene has not been approved in the United States. Bazedoxifene emerged from *in-vitro* screens that selected for compounds that bound to ER and competitively displaced 17β-estradiol, inhibited estrogen action in estrogen models and did not manifest ERα agonist activity in contexts where tamoxifen functions as an agonist, as in the endometrium.

Based on *in-vitro* studies, bazedoxifene does not stimulate MCF7 breast cancer cell proliferation and suppresses breast cancer cell proliferation induced by 17β-estradiol in a dose dependent manner [23]. In animal studies, treatment with bazedoxifene preserved bone mass and bone strength and decreased levels of bone turnover markers. In immature rats, bazedoxifene protected against estrogen-stimulated increases in uterine wet weight. In mice it was a more effective antagonist against conjugated estrogen induced stimulation of the mammary gland compared to other SERMs [24]

Bazedoxifene Preclinical Data

Preclinical studies show that bazedoxifene inhibits estrogen induced cell growth in ER+ breast cancer cell lines with an IC50 of 0.19nM. This inhibition is due to antagonistic effect of bazedoxifine on ER, as the growth

effect is lost with ER knock-down by siER. In addition, bazedoxifene also inhibits the ligand independent cell growth of clonally derived long-term estrogen deprived cells, a cellular model of aromatase inhibitor resistance. Fulvestrant also has an inhibitory effect on these resistant cells but requires a higher concentration. Additionally, bazedoxifene induces G1-phase cell cycle block by directly reducing Cyclin D1 levels [25]. Breast cancer xenograft studies showed that bazedoxifene inhibits tumor growth and reduced tumor doubling time. Similarly, in a tamoxifen resistant breast cancer xenograft model in which growth is stimulated by tamoxifen, bazedoxifene treatment reversed the tamoxifen stimulation of these tumors and led to tumor regression [26].

Both *in-vitro* and *in-vivo* studies show that bazedoxifene has SERD activity, which is proteasome dependent. Furthermore, in the presence of bazedoxifene, ER mRNA levels do not increase in response to increased ER degradation, resulting in sustained knock-down of ER over time in the absence of a feedback mechanism to restore receptor levels [26].

Bazedoxifene Pharmacokinetic (PK) data

Pharmacokinetic studies were conducted in healthy post-menopausal women. In one study, women received multiple doses of 5, 20 and 40 mg bazedoxifene daily in a randomized crossover fashion for 14 days. The maximum concentration (C_{max}) was dose dependent and was reached within 1-2 hours. The half-life of bazedoxifene was 28 hours. Bazedoxifene exhibited linear pharmacokinetics. Plasma concentrations were approximately double at steady state, which was reached by day 7. Protein binding was greater than 99%. Results from a metabolic disposition study showed that the major route of excretion was feces (85%), with less than 1% excreted in the urine. The major metabolic pathway was glucuronidation, with little or no cytochrome P450 metabolism.

Bazedoxifene Dose Rationale

Bazedoxifene has been tested in a 2 part, 6 month, double blind, randomized, active and placebo controlled study that included 497 healthy post-menopausal women. Conjugated estrogen (0.625 mg)/ medroxy-progesterone actetate (2.5) was the active control. Bazedoxifene doses in the first part included daily 2.5 mg, 5mg, 10mg and 20mg and in the second part daily 20mg (n=60), 30mg (n=60) and 40mg (n=60) [27]. Endometrial thickness was monitored closely and doses 2.5 -20mg/ day resulted in no significant endometrial thickness changes compared to placebo. The 30 and 40mg/day doses were associated with a decrease in endometrial thickness, which was inversely related to dose. None of the endometrial biopsy specimens demonstrated endometrial hyperplasia. The most commonly reported adverse events were: abdominal pain, headache, breast pain and flu syndrome. One possible related serious adverse event was an episode of supraventricular tachycardia after a concomitant use of a salbutamol inhaler.

A double-blind, placebo-controlled, ascending multiple-dose safety and tolerability study of bazedoxifene was conducted including 107 healthy postmenopausal women (information from Pfizer). Fifteen (15) subjects (12 to receive Bazedoxifene and 3 to receive placebo) participated in each of the 7 dose groups. The 7 oral doses of Bazedoxifene were 1, 2.5, 5, 10, 20, 40, and 80 mg, given once daily for 30 consecutive days. One (1) or more adverse events were reported by 78 (73%) subjects; 10 (77%) who took Bazedoxifene 1 mg, 8 (62%) who took Bazedoxifene 2.5 mg, 7 (58%) who took Bazedoxifene 5 mg, 9 (75%) who took Bazedoxifene 10 mg, 9 (75%) who took Bazedoxifene 20 mg, 10 (83%) who took Bazedoxifene 40 mg, 8 (67%) who took Bazedoxifene 80 mg, and 17 (81%) who took placebo. The majority of adverse events (82%) were reported as mild and 18% were reported as moderate. There were no severe adverse. Of the 78 subjects who reported adverse events, 43 (55%) reported adverse events that were considered as possibly, probably, or definitely drug-related by the investigator, and 35 (45%) that were considered as not drug-related. The most frequently reported adverse events were: headache reported by 19 subjects (18%), constipation reported by 13 (12%) subjects, accidental

injury reported by 10 (9%) subjects, and dizziness, pharyngitis, and nausea, each reported by 7 (7%) subjects. No overall differences between treatment groups and no dose-related differences in the frequency were observed.

A 2-year phase III, double blind, randomized study was performed to study the efficacy of bazedoxifene in the prevention of osteoporosis. In this study bazedoxifene was found to significantly prevent bone loss. A total of 1583 healthy post-menopausal women with osteoporosis risk were randomized to receive daily bazedoxifene 10 (n=321), 20 (n=322) or 40mg (n=319), raloxifene 60mg or placebo. All doses of bazedoxifene were generally well tolerated and exhibited a safety profile generally similar to that of placebo. The most common adverse events in all treatment arms were headache, infection, arthralgia, pain, hot flashes and back pain. Hot flashes were more common in all doses of bazedoxifene (ranging from 19.6-24.1%) compared to placebo (14.2%), but similar to raloxifene. Four deaths were reported during the study and two deaths were reported after withdrawal or completion of the study. Five of the deaths were not considered related to the administered treatment. One death in the bazedoxifene 40mg arm, a subject experienced a pulmonary embolism during a prolonged air flight 30 days after study completion, was considered by the investigator to be possibly related to treatment. There were no cases of endometrial hyperplasia or endometrial cancer in the bazedoxifene groups. There were significant increases in triglyceride levels in all bazedoxifene treated arms, but the number of subjects that developed hypertriglyceridemia was low (0.3-1.6%) [28].

A 3-year randomized phase III, double blind, randomized study was conducted in women with osteoporosis to assess the efficacy of bazedoxifene in reducing new vertebral fracture risk. A total of 7492 women were randomized to daily bazedoxifene 20mg (n=1886) or 40mg (n=1872), raloxifene 60mg or placebo. Bazedoxifene was shown to reduce the risk of vertebral fractures. Both doses of bazedoxifene were well tolerated. The incidence of adverse events, serious adverse events, and deaths were generally similar to that in the placebo group. The incidence of venous thromboembolic events (deep venous thrombosis/ pulmonary embolism) was higher in the treatment arms compared with the placebo arm (bazedoxifene 20 mg, 0.7%; bazedoxifene 40mg, 0.6%, raloxifene 60mg 0.5% ; placebo 0.3%). The frequency of the development of breast cancer was lower in the bazedoxifene treatment arms relative to the raloxifene and placebo arms [29].

The 40mg dose of bazedoxifene was chosen for this study given the extensive data of the safety of this dose in over 2000 patients, as described in the studies above, and the pre-clinical evidence of improved ER degradation and antagonistic activity with increasing doses of bazedoxifene (figure 1). Furthermore, several recent clinical studies have shown, that in metastatic disease, improved ER inhibition by increasing the dose of fulvestrant or combining fulvestrant with an aromatase inhibitor can result in improved clinical outcomes [30, 31]. Taken together, these studies suggest that a higher dose of bazedoxifene could have increased efficacy without added toxicity.

2.3 Rationale

Combination of bazedoxifene with palbociclib: The combination of palbociclib and letrozole is a very promising regimen for the treatment of metastatic HR+ breast cancer. However, many patients with ER+ breast cancer receive an aromatase inhibitor as part of adjuvant hormonal therapy or as a single agent as first line treatment in the metastatic setting. A combination of palbociclib with an endocrine treatment of a different class is lacking and may be superior.

Fulvestrant is an endocrine treatment that is a SERD and has a different mechanism of action compared to aromatase inhibitors. Fulvestrant is an approved drug for the treatment of aromatase inhibitor refractory disease and the combination of palbociclib with fulvestrant is a potential regimen. However, the response rate to fulvestrant in the setting of refractory disease is approximately 10%, similar to exemestane, as a second line steroidal aromatase inhibitor. The low efficacy of fulvestrant is likely not to due to its mechanism of action but

rather, the pharmacokinetic properties of fulvestrant, which is administered by intramuscular injection, is the limiting factor. Indeed, despite the use of higher loading doses, drug concentrations measured in the vicinity of the tumor were found to be insufficient to saturate ER [32]. In addition, positron emission tomography studies confirmed poor delivery of fulvestrant to the tumor. Higher doses of fulvestrant were shown to be associated with improved progression free survival and the 500mg dose of fulvestrant is now the standard of care [31]. Despite this improvement in the delivery of fulvestrant, it is likely, that the full therapeutic potential of SERD treatment has not been revealed with this drug.

Bazedoxifene is an orally bioavailable SERM with SERD activity [33,34]. *In-vitro* and *in-vivo* studies show that bazedoxifene inhibits cellular proliferation and tumor growth similarly to fulvestrant. The bioavailability of bazedoxifene is likely pertinent to evaluate the full potential of a SERD in the treatment of refractory disease. In addition, bazedoxefine was shown to directly inhibit cyclin D1 and therefore bazedoxifene may potentiate the activity of palbociclib [34].

We confirmed that bazedoxifene functions both as an ER antagonist and ER degrader. As shown below, we detected similar ER degradation levels when bazedoxifene was compared to fulvestrant. In contrast, when we looked at the inhibition of ER activity by using MCF7 cell stably infected with an ERE-luciferace promoter-reporter construct, bazedoxifene displayed improved ER inhibition compared to fulvestrant (fig.1). In addition, our preliminary data in three different ER+ breast cancer cell lines show that single agent fulvestrant and bazedoxifene alone inhibit cell growth comparably. However, the combination of palbociclib with either fulvestrant or bazedoxifene inhibits cell growth in a synergistic manner, with the latter combination being significantly superior. We also tested the growth effects of the different treatments in long-term estrogen deprived (LTED) cell lines. In this cell line that models resistance to aromatase inhibitors, we saw that the combination of palbociclib with bazedoxifene also had synergistic activity.

2.4 Correlative Studies Background

The correlative studies proposed in this protocol are exploratory and hypothesis-generating. Promising hypotheses may be further explored and/or validated in future studies.

- To explore whether high levels of cyclin D1, Rb and/or phosphorylated Rb or low levels of p16, p27 are associated with objective response
- To explore whether patients harboring a *ESR1* mutation respond to the combination of palbociclib with bazedoxifene.
- To explore if there is an association between genetic alterations most frequently found in hormone receptor positive breast cancer and objective response or overall survival by performing Next Generation Sequencing (NGS) in archival metastatic tumor samples and/or prospectively collected metastatic samples.
- Study mechanisms of resistance by studying expression levels of ER, Cyclin D1, phosphorylated Rb and the Cdk inhibitors p21, p27 and p16, EGFR, and phosphorylated AKT as well as targeted NGS of tumors attained after the development of resistance.
- To explore the sensitivity of plasma cell free DNA (cfDNA) and droplet digital PCR (ddPCR) to detect mutations in metastatic breast cancer.
- To analyze if changes in levels of mutations as determined by plasma cfDNA and ddPCR correlate with response or resistance to treatment.

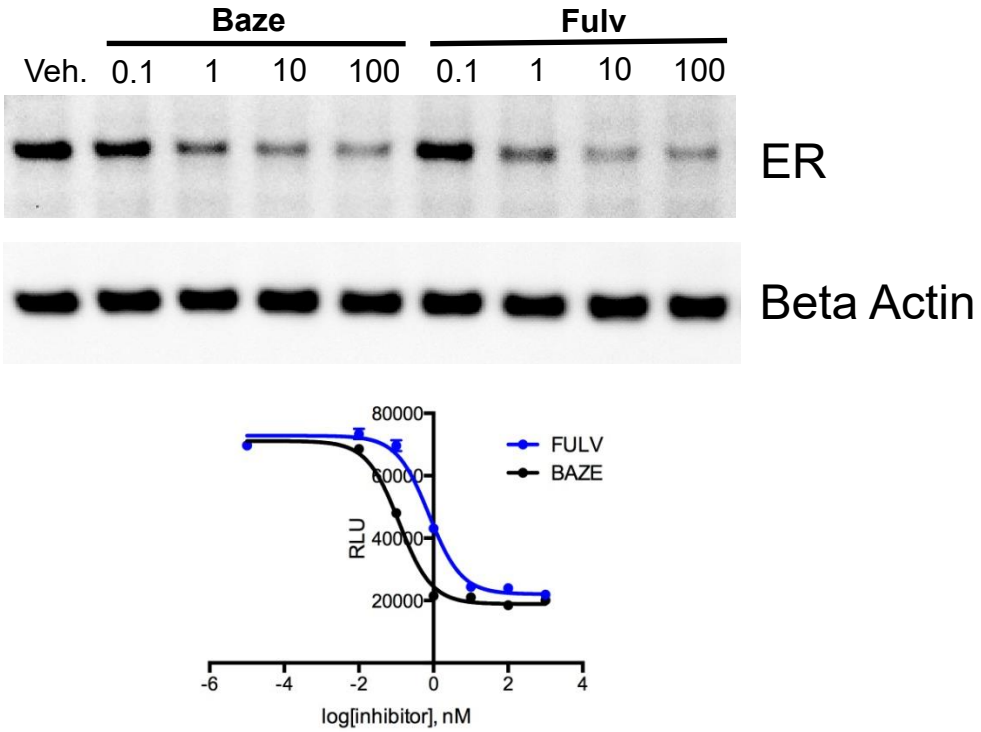


Fig. 1: **Bazedoxifene activity compared to fulvestrant:** Above: ER levels in MCF7 cells treated with increasing doses of bazedoxifene or fulvestrant (nM).
Below: dose response curve of luciferase activity in MCF7 cells with stable expression of ERE-luciferase. Bazedoxifene IC50=0.12 nM, fulvestrant IC50=0.76nM.

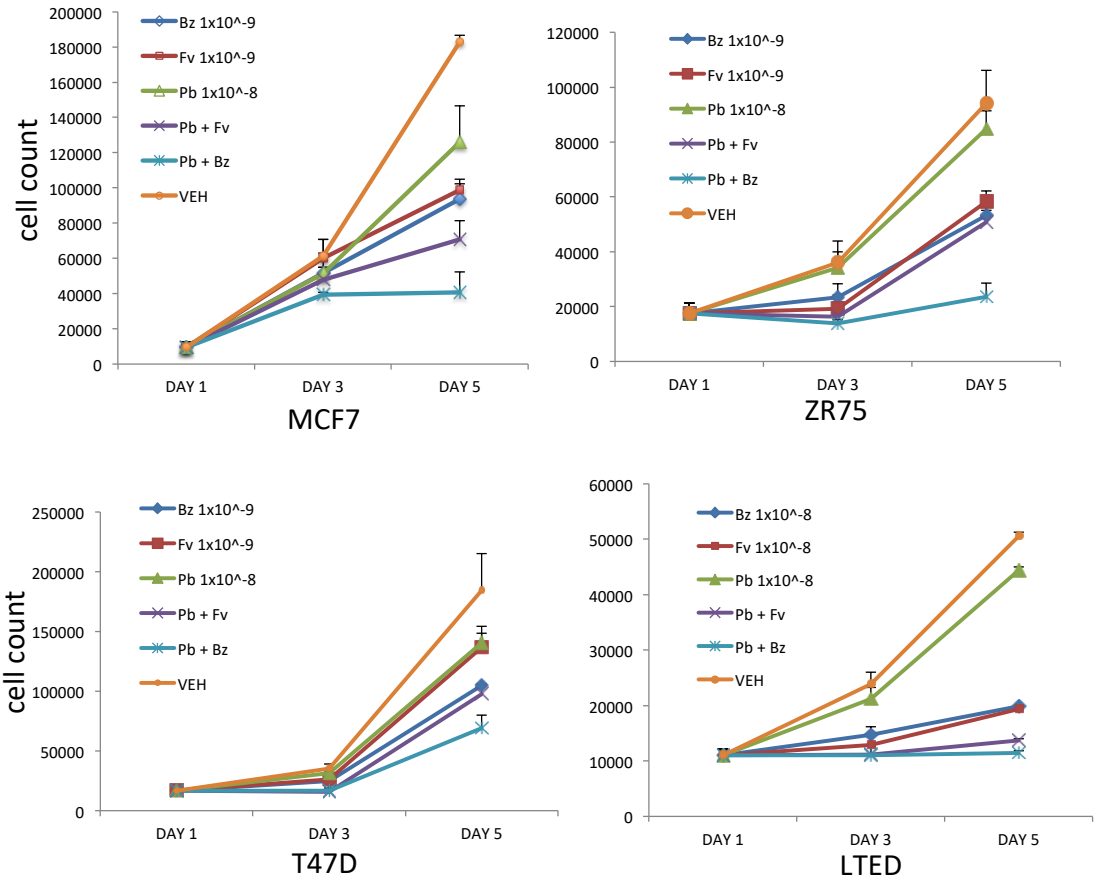


Fig. 2: **Cell growth curves:** cell count analysis on days 1,3 and 5 of treatment in MCF7, ZR75 and T47D cells. LTED=long term estrogen deprived, Bz=bazedoxifene, Fv=fulvestrant, Pb=palbociclib, VEH=vehicle. Doses are in nM.

2.4.1 Cyclin D1,Rb, phosphorylated Rb p16 and p27 levels in archival, metastatic and time of progression samples

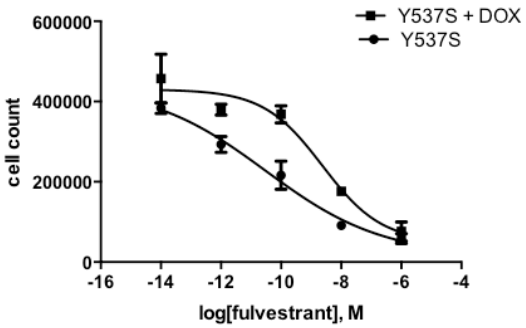
Cyclin D1 level was tested in the phase II study PALOMA-1 and was not found to correlate with benefit from palbociclib. Therefore we will test additional proteins that are key proteins related to the CDK4/6-cyclinD1 complex and might predict response to treatment. These proteins will be studied by immunohistochemistry (IHC) in archival tissue samples from the primary tumors and metastatic samples in order to test if the expression levels of these proteins are concordant and if both tissue sources can be utilized for the evaluation of these biomarkers.

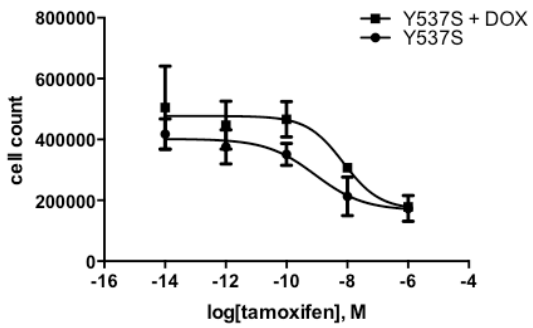
2.4.2 *ESR1* Mutations

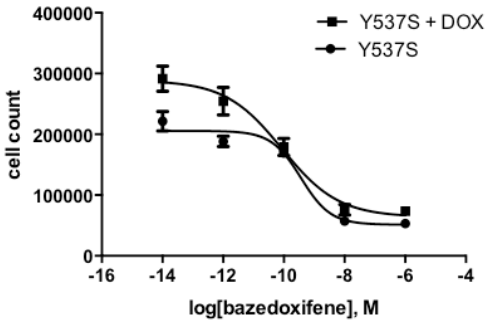
We and other groups recently identified *ESR1* mutations in approximately 15% of patients with metastatic ER+ breast cancer. In all studies, the *ESR1* mutations are located in a hot spot in the ligand-binding domain [5-9]. In our study, *ESR1* mutations were not detected in primary ER+ breast cancers and all patients harboring a mutation received at least one line of hormonal therapy. Additionally, we found a correlation between the mutation frequency and number of treatment lines in the metastatic setting; patients who received at least 3 lines of treatment in the metastatic setting had a 20% mutation frequency. Our pre-clinical data in ER+ breast cancer

cell lines show that these mutations confer constitutive activity and relative resistance to tamoxifen and fulvestrant. Taken together, these results suggest the clonal selection of *ESR1* mutations that render endocrine resistance in metastatic ER+ breast cancer.

We hypothesize that the combination of bazedoxifene and palbociclib may be effective in overcoming treatment resistance mediated by the *ESR1* mutations. This hypothesis stems from pre-clinical data suggesting that SERDs can inhibit tumor growth driven by *ESR1*, but higher doses are required. Given the oral bioavailability of bazedoxifene, this might be achieved with this agent. In addition, since cyclin D1 is one of the key proteins regulated by the ER and downstream to the mutation, it is an attractive target for overcoming resistance mediated *ESR1* mutations. As shown in Figure 3, employing MCF7 cells lines with doxycycline induced *ESR1* mutations, we confirmed that the mutations confer relative resistance to tamoxifen and fulvestrant. In contrast, ER mutant cells remain sensitive to bazedoxifene, further supporting the rationale of this study.







	Y537S IC50 (M)	
	No DOX	+DOX
Fulvesrant	3.0x10^-11	2.4x10^-9
Tamoxifen	8.6x10^-10	7.4x10^-9
Bazedoxifene	3.6x10^-10	8.7x10^-11

Fig 3: **Improved growth inhibition of ER mutants by bazedoxifene:** Dose response curves and IC50 levels for cell growth in MCF7 cell with doxycycline inducible Y537S *ESR1* mutation at day 5 of treatment. DOX= doxycycline .

2.4.3 Whole exome next generation Sequencing

The major advances in genomic sequencing capacity have enabled the completion of several large whole exome sequencing studies of primary breast cancer. In the TCGA study, luminal breast cancers were found to harbor the most significantly mutated genes, which could explain the high molecular and clinical heterogeneity of this breast cancer subtype. The most commonly altered genes in primary luminal-type breast cancers include; *PIK3CA, TP53, MAP3K1, MAP2K4, GATA3, MLL3, CDH1, PTEN, NCOR1, FOXA1, ERBB2*. The functional roles of these mutations in the development and progression of metastatic ER+ breast cancer have not been elucidated yet and whole exome sequencing studies of metastatic breast cancer are limited. Therefore, in this study we will perform whole exome sequencing of archival primary and metastatic samples as well as prospectively collected metastatic samples, in order to study the associations between mutations and response to

treatment. In addition, we and other groups detected *ESR1* mutations in metastatic ER+ breast cancers of patients who developed endocrine resistance. In this study we will also study the *ESR1* mutations in the tissue specimens to test if there is an association between these mutations and response. As part of this study, we will analyze germline DNA from blood samples in order to confirm that the mutations detected in the tumor specimens are somatic mutations.

2.4.4 Study mechanisms of resistance to palbociclib and bazedoxifene

Metastatic tissue samples from patients who developed progressive disease will also be biopsied. These samples with be analyzed by IHC and whole exome NGS to study changes in protein expression and genomic alterations that are associated with the development of resistance to treatment.

2.4.5 Cell-free DNA

Tumor genotyping using cell-free plasma DNA (cfDNA) has the potential to enable non-invasive assessment of genetic alterations that are predictive of either response or resistance to a given treatment. Recently, the Janne lab has published the use of ddPCR of cfDNA to detect and quantify mutations in advanced lung cancer and melanoma [33]. Serial plasma genotyping of the lung cancer EGFR mutant in patients treated with erlotinib demonstrated pre-treatment detection of EGFR mutations, complete plasma response in most cases and increasing levels of mutations that confer resistance prior to the development of objective progression.

In this study, plasma will be collected prior to treatment and with each cycle. cfDNA will be extracted and *PIK3CA, ESR1, TP53, GATA3,NCOR1* and *ERBB2* mutations will be assessed. Serial plasma samples will allow us to follow correlations between mutational changes as detected in cfDNA and response to treatment.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically confirmed invasive breast cancer that is metastatic or unresectable locally advanced. Histological documentation of metastatic/recurrent breast cancer is not required if there is unequivocal evidence for recurrence of the breast cancer.

3.1.2 Estrogen and/or progesterone receptor positive breast cancer (>10% staining), as determined by pathology from either primary or metastatic site(s). Central confirmation is not required.

3.1.3 HER2 negative, defined as 0-1+ by immunohistochemistry or FISH-negative (HER2 copy number <6 and HER2/CEP17 ratio < 2.0). Central confirmation is not required.

3.1.4 Postmenopausal women are eligible. Postmenopausal is defined as any of the following:

- Age ≥ 60 years
- Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range.
- Premenopausal women who have been on a GnRH agonist for at least 3 consecutive months prior to study entry are eligible. Women in this group MUST remain on the GnRH agonist for the duration of protocol treatment.

- Status-post bilateral oophorectomy-After adequate healing post surgery.

3.1.5

Women age ≥ 18 years of age. Men are excluded

Because no dosing or adverse event data are currently available on the use of palbociclib and bazedoxifene in participants <18 years of age, children are excluded from this study. In addition, breast cancer is exceedingly rare in individuals under 18 years of age.

3.1.6 Participants must have measurable disease by RECIST 1.1. See section 11 for the definition of measurable disease.

3.1.7 Bone only disease if there are lytic lesions is also allowed and treatment response will be evaluated based on the MD Anderson criteria. See section 11.

3.1.8 Endocrine resistant breast cancer, defined as either:

- Relapsed while on adjuvant endocrine therapy or within 1 year of completion of adjuvant endocrine therapy

  -or-
- Progression through at least one line of endocrine therapy for metastatic or locally advanced breast cancer. There is no limit on the number of prior endocrine therapies received.

3.1.9 Patients may have received up to one prior line of chemotherapy for metastatic or unresectable locally advanced breast cancer.

3.1.10 Patients may have initiated bisphosphonate therapy prior to start of protocol therapy. Bisphosphonate therapy may continue during protocol treatment. Such patients will have bone lesions considered evaluable for progression

3.1.11 Patients must be at least 2 weeks from prior chemotherapy, including biologics or targeted therapy (i.e. everolimus), or radiotherapy, or any investigational drug product, with adequate recovery of toxicity to baseline, or grade <1, with the exception of alopecia and hot flashes. There is no washout period for prior endocrine therapy.

3.1.12 ECOG Performance Status 0-1 (Appendix A)

3.1.13 Life expectancy of greater than 3 months

3.1.14 Willingness to undergo research biopsy under the following circumstances:

- Patients with "easily accessible disease"

  - Patients with skin or chest wall disease amenable to a punch biopsy under local anesthesia are required to undergo a baseline biopsy and a biopsy at the time of disease progression as part of this protocol.
  - Patients with a breast mass or axillary lymph node amenable to an image-guided core biopsy are also required to undergo a baseline biopsy and a biopsy at the time of disease progression as part of this protocol.
  - Patients with malignant ascites fluid or a malignant pleural effusion of sufficient volume to be amenable to tap (either in-office or image-guided) are also required to undergo a baseline tap and a tap at the time of disease progression as part of this protocol.

- Patients who undergo a research biopsy procedure for the purpose of this protocol, and in whom inadequate tissue is obtained, *are still eligible* and are not required to undergo a repeat biopsy in order to enter the study.
- Patients will be approached during cycle 1 about providing an optional tissue sample at that time; however, this biopsy will be optional.

- Patients with "accessible disease"

  - Patients with sites felt to be accessible to an image-guided or incisional biopsy in the opinion of the patient's treating oncologist and physician performing the procedure, and not meeting the criteria for "easily accessible disease" as described in Section 3.1.14.1, are required to undergo a baseline biopsy as part of this protocol. Such sites may include, but are not limited to: liver, lymph nodes, soft tissue, lung, chest wall, and bone. Cycle 1 biopsy and biopsy at time of disease progression are optional.
  - Biopsies may be done with local anesthesia or intravenous conscious sedation, according to standard institutional guidelines.
  - If a biopsy requires general anesthesia, then it is only allowed if acquisition of tissue is necessary for clinical reasons (i.e. is clinically indicated), and excess tissue that would otherwise have been discarded is then used for research purposes. If a biopsy requires general anesthesia, then a biopsy of that site for research purposes only, *without* a coexisting clinical indication is not allowed on this protocol.
  - Patients who undergo a research biopsy procedure for the purpose of this protocol, and in whom inadequate tissue is obtained, *are still eligible* and are not required to undergo a repeat biopsy in order to enter the study.
  - Some patients may have had a clinically indicated biopsy upon recent disease progression. No additional pre-treatment biopsy is required if that specimen can be used for the correlative studies described in this protocol.
  - Patients will be approached at the time of progression about providing an optional tissue sample at that time; however, the time of progression biopsy will be optional.

- Other patients

Patients who do not have biopsy-accessible disease are not required to undergo a biopsy as part of study participation.

In addition, patients who are being treated with therapeutic doses of anticoagulant(s), are not required to undergo a biopsy as part of study participation. If it is felt clinically appropriate despite anticoagulation (i.e. a skin punch biopsy, etc) by the treating physician, a biopsy is allowed, it is simply not required.

The sites of metastatic disease and reason that the disease is not biopsy-accessible should be documented in the medical record and case report form(s).

Patients who do not undergo baseline biopsy must have their study participation approved by the overall PI before start of protocol therapy. Only patients who have biopsy inaccessible disease may enter the study without the requirement for baseline biopsy.

3.1.15 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count $\geq$ 1,500/mcL
- Platelets $\geq$ 100,000/mcL

- Hgb $\geq$ 9 g/dL (which may be post transfusion)
- Total bilirubin $\leq$ 1.5 X institutional upper limit of normal (patients with
    - documented Gilbert's disease are allowed total bilirubin up to 3X ULN)
- AST (SGOT)/ALT (SGPT) $\leq$ 2.5 X institutional upper limit if no liver metastases; and $\leq$ 5 X institutional upper limit if liver metastases are present.
- Creatinine $\leq$ 2X institutional upper limit of normal
- Baseline QTc $\leq$ 480 ms

3.1.16 Ability to take oral medications.

3.1.17 The effects of palbociclib and bazedoxifene on the developing human fetus are unknown. If, for any reason, a woman should become pregnant or suspect that she is pregnant while participating in this study, she should inform her treating physician immediately.

Women who are made postmenopausal through use of GNRH agonists, and men are required to use adequate contraception for the duration of protocol treatment and for 6 months after the last dose of palbociclib and bazedoxifene. Adequate contraception is defined as one highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner.

Highly Effective Non-Hormonal Contraception Methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are considered highly-effective forms of contraception. The following non-hormonal methods of contraception are acceptable:

- True abstinence when this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception].
- Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomized male partner should be the sole partner.

OR

Effective Non-Hormonal Contraception
Alternatively two of the following effective forms of contraception may be used instead:

- Placement of non-hormonal intrauterine device (IUD) or intrauterine system (IUS). Consideration should be given to the type of device being used, as there is higher failure rates quoted for certain types, e.g., steel or copper wire.
- Condom with spermicidal foam/gel/film/cream/suppository.
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of spermicide.

The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection.
- However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

It should be noted that two forms of effective contraception are required. A double barrier method is acceptable, which is defined as condom and occlusive cap (diaphragm or cervical/ vault caps) with spermicidal foam/gel/film/cream /suppository. Premenopausal women who have been on a GnRH agonist for at least 3 consecutive months prior to study entry are eligible. Women in this group MUST remain on the GnRH agonist for the duration of protocol treatment. Such patients should be counseled that GnRH agonists alone may not be adequate contraception and that adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation should be employed.

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

3.2 Exclusion Criteria

3.2.1 Prior treatment with a CDK4/6 inhibitor and/or bazedoxifene.

3.2.2 Participants may not be receiving any other investigational agents.

3.2.3 Concurrent treatment with commercial agents or other agents with the intent to treat the participant's malignancy, including endocrine therapy, chemotherapy, and/or targeted therapy, with the exception of bisphosphonates and GnRH agonists, as detailed in sections 3.1.4 and 3.1.9.

3.2.4 Untreated or progressive brain metastases. Patients with treated brain metastases not requiring chronic corticosteroids for symptom control are eligible.

3.2.5 Pending visceral crisis, in the opinion of the treating investigator.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to palbociclib and /or bazedoxifene.

3.2.7 Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A isoenzymes are ineligible. Lists including medications and substances known or with the potential to interact with the CYP3A isoenzymes are provided in Appendix C. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.8 Current use of drugs that are known to prolong the QT interval (See Appendix B)

3.2.9 Subjects with organ allograft requiring immunosuppression.

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

3.2.11 Pregnant women are excluded from this study because effects of palbociclib and bazedoxifene on a developing fetus is unknown. Breastfeeding should be discontinued prior to entry onto the study.

3.2.12 Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: ductal carcinoma *in situ* of the breast, cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.

3.2.13 Patients on combination antiretroviral therapy, i.e. those who are HIV-positive, are ineligible because of the potential for pharmacokinetic interactions or significant immunosuppression with Palbociclib.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. Every effort will be made to include patients from minority populations.

4. REGISTRATION AND RECRUITMENT PROCEDURES

4.1 Recruitment Procedures

To enhance accrual and awareness of the trial, the study team will review clinic schedules and patient lists of medical oncologists at DF/HCC to identify eligible patients with hormone receptor positive breast cancer.

Providers will be contacted about any patients identified through this procedure and given the opportunity to consider this patient for treatment on trial, and subsequently approach the patient about participating in the trial.

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

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

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

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

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

  Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for a treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

5. TREATMENT PLAN

Bazedoxifene and palbociclib will be supplied every 4 weeks, with 28 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for palbociclib are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The safety run-in phase of the study will include six patients. If more than 1 of 6 patients has a dose limiting toxicity the dose will be reduced to 100 mg for the remainder of the study. Accrual to the study will be paused for official safety analysis after all six patients complete at least one treatment cycle.

5.1 Treatment Regimen

Regimen Description					
Agent	**Premedication; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Palbociclib	Given with food	125 mg[a]	PO	Daily on days 1-21, followed by one week off	28 days (4 weeks)
Bazedoxifene	None	40mg	PO	Daily, Continuous	

a. If more than 1 of 6 patients has a dose limiting toxicity in the safety run, the dose will be reduced to 100mg for the remainder of the study.

5.2 Pre-Treatment Criteria

Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments. If screening assessments occur within 3 days before start of study treatment, then they may serve as the baseline Cycle 1 Day 1 study tests.

Pretreatment criteria will be assessed within 14 days of the first dose of study treatment to establish eligibility and baseline values. This will be considered the baseline clinical evaluation. Subsequent changes from screening physical exam (PE) findings that meet the definition of an AE will be recorded on the AE page of the eCRFs.

Demographic information and baseline characteristics will be collected at the Screening Visit. Standard demographic parameters include age, sex, and race/ethnicity (recorded in accordance with prevailing regulations). Baseline characteristics will include ECOG PS (Appendix A), disease status, medical histories, prior and concomitant medications, and PE findings. Relevant hormone receptor status will be collected.

Additional pre-treatment evaluations, also found in section 3.1, are CBC with differential, chemistries, and EKG.

Required results for initiation of protocol therapy include:

- Absolute neutrophil count $\geq$ 1,500/μL
- Platelets $\geq$ 100,000/μL
- Hemoglobin $\geq$ 9g/dL
- Total bilirubin $\leq$ institutional upper limit of normal (patients with documented Gilbert's disease are allowed total bilirubin up to 1.5X ULN)
- AST (SGOT)/ALT (SGPT) $\leq$ 2.5 X institutional upper limit of normal
- Creatinine within normal institutional limits or creatinine clearance > 60 mL/min/1.73 m_2 for subjects with creatinine levels above institutional normal.
- Baseline QTc $\leq$ 480 ms
- Pregnancy test for women on a GNRH analog.
- FSH and estradiol for women <60 who have had amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression)

5.3 Agent Administration

5.3.1 Palbociclib

Palbociclib 125 mg should be taken orally, once per day, with food. If a dose is vomited, a replacement dose should NOT be taken. If a dose is missed, and it is less than 6 hours from usual time of dosing, then patients may take that dose. Otherwise that dose should be skipped and NOT retaken; patients should resume regular dosing the following day. Patients who inadvertently take 1 extra dose during a day must skip the next day's dose. Patients should be instructed to record daily administration of the study drugs in a drug diary (Appendix D). Treatment is continuous daily for 21 days, and then 7 days off, to complete a 28 day cycle.

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

To be considered compliant, each study patient must have taken at least 80% of the planned number of doses of primary therapy based on the number of days of actual dose administration.

5.3.2 Bazedoxifene

Bazedoxifene 40mg (2 tabs of 20mg) should be taken orally, once per day. If a dose is vomited, a replacement dose should NOT be taken. If a dose is missed, and it is less than 6 hours from usual time of dosing, then patients may take that dose. Otherwise that dose should be skipped and NOT retaken; patients should resume regular dosing the following day. Patients who inadvertently take 1 extra dose during a day must skip the next day's dose. Patients should be instructed to record daily administration of the study drugs in a drug diary (Appendix D).

Treatment is continuous daily to complete a 28 day cycle. Ordering of bazedoxifene self-administration relative to palbociclib self-administration is as per patient preference.

On days when patient is scheduled for a clinic visit, the patient may take the oral medications at home or in the clinic.

In addition, patients will bring pill blister cards to visits, and pill counts will be performed as follows: Patients will be required to return all blister cards of bazedoxifene as well as the completed drug diary at each study visit for drug accountability. Drug accountability for bazedoxifene will be performed at each study visit prior to dispensing drug supply for the next cycle(s). The number of remaining capsules/tablets will be documented and recorded.

To be considered compliant, each study patient must have taken at least 80% of the planned number of doses of primary therapy based on the number of days of actual dose administration.

5.4 General Concomitant Medication and Supportive Care Guidelines

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 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
- Agents to assist in the management of hot flashes or headaches (NSAIDs, gabapentin, duloxetine, venlafaxine, citalopram, etc)
- Treatment with either a bisphosphonate or denosumab when bone lesions are documented (as non-target lesions) is allowed for the treatment of bone metastases. The first dose should be given prior to the start of protocol therapy. Oral bisphosphonate treatment is allowed for patients with a low bone mineral density. Patients already receiving bisphosphonate at the time of study entry can continue the treatment.
- Growth Factors: Patients may receive erythropoietin while on study, at the discretion of the patient's treating physician. The use of G-CSF/GM-CSF should generally be limited to clinical scenarios such as febrile neutropenia or active infection, and should not be administered on a chronic basis to maintain neutrophil counts as part of ongoing therapy. The use of platelet growth factors are specifically prohibited on this protocol. Please consult the Principal Investigator with questions. Investigational growth factors are not permitted on this study.

The use of concurrent investigational or other antitumor therapies is not permitted. Missed doses of either endocrine therapy or palbociclib 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. The concurrent use of CYP3A inducers, including carbamazepine, felbamate, nevirapine, phenytoin, primidone, rifabutin, rifampin, rifanpicin, rifapentin, and St. John's wort, are not allowed in the study. This medication list may also be found in Appendix C.

Concomitant use of moderate CYP3A inducers and CYP3A substrates is allowable on study, however precaution should be exercised for use of any concomitant medication.

Uridine diphosphate glucuronosyltransferase (UGT) inducers are not allowed in this study. Bazedoxifene is a UGT substrate. Co-administration with drugs that are UGT inducers may change the plasma concentrations of bazedoxifene. The concurrent use of the UGT inducers carbamazepine, dabrafenib, eslicarbazepine acetate, phenobarbital, phenytoin and rifampin are not allowed in the study.

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 and bazedoxifene therapy 7 days before the surgery and up to 3 weeks after surgery. Patients may resume palbociclib and bazedoxifene therapy once satisfactory wound healing and recovery have occurred.

Proton pump inhibitors (PPI) may be taken while on study, however it is recommended that the PPI is taken 12 hours from the time of palbociclib administration. 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.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

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

At the time the patient is taken off study treatment, alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Dr. Rinath Jeselsohn at 617-632- 3352, pager #42912 (Email: rjeselsohn@partners.org).

5.6 Duration of Follow Up

Participants will be followed approximately every 4 months for up to 2 years after going off treatment or until death, whichever occurs first. Participants who have been taken off treatment for unacceptable adverse events will be followed at least until resolution or stabilization of the adverse event.

5.7 Criteria for Removal from Study Follow-up

Participants will be removed from follow up when any of the criteria listed in Section 5.5 applies. The reason for removal from study follow up and the date the participant was removed must be documented in the study-specific case report form (CRF).

Participants who are removed from study treatment will continue to be followed for long-term outcomes for up to 2 years as specified in Section 5.6.

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

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

- Death

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from study. This form can be found on the QACT website or obtained from the QACT registration staff.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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.

6.1 Toxicity Management

6.1.1 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 6.2.3. 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 6.2.1) 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 and bazedoxifene treatment.

Patients discontinuing palbociclib and/or bazedoxifene treatment due to treatment-related toxicity will come off study.

6.1.2 Toxicity management – Bazedoxifene

No dose reduction for bazedoxifene is permitted, but dosing interruptions are allowed (see section 6.2).
Treatment interruptions for up to 3 cumulative weeks for bazedoxifene related toxicities or personal reasons are allowed as per the investigator's best medical judgment. Patients discontinuing due to treatment-related toxicity will discontinue protocol therapy and come off study.

6.2 Dose Modifications/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.

6.2.1 Palbociclib Dosing Interruptions/Delays

Patients experiencing the following adverse events should have their treatment of palbociclib interrupted/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 2 or higher thrombocytopenia (Platelet <75,000/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 and bazedoxifene will be permanently discontinued.

Patients should not hold or discontinue palbociclib for side effects potentially or likely related to concomitant bazedoxifene as per the investigator's judgment. Appropriate follow up assessments should be performed until adequate recovery occurs as assessed by the Investigator before treatment can resume.

Missed doses are not made up. When the adverse event resolves, the cycle will continue as scheduled. 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 principal investigator. If a dose reduction is applied, the patient may need to return to the clinic to receive new drug supply.

6.2.2 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/mm3 and no fever
- Any persistent grade 2, grade 3 or higher treatment-related non-hematologic AEs considered related to palbociclib have recovered to Grade ≤ 1 or baseline.
- 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.

Cycles should be 28 days long even if the start of a new cycle is delayed.

Doses missed within a cycle are not made up. If the adverse event resolves before the end of the cycle then the patient can resume taking the Palbociclib for the remainder of the cycle but should still stop on Day 21 to maintain the 7- day break.

The start of a new cycle should be delayed if an adverse event requiring a dose hold has not resolved by Day 1.

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 principal investigator. If a dose reduction is applied, the patient may need to return to the clinic to receive new drug supply.

If these parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should be removed from the study.

6.2.3 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. Dose reduction of palbociclib by one dose level, and, if needed, by two dose levels (Table 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. Dose re-escalation is not allowed. Patients requiring more than 2 dose reductions will be discontinued from the study.

Table 1. Dose Levels

Dose Level	**Palbociclib for 3 out of 4 weeks (3/1 schedule)**
Starting dose	125 mg /day
-1	100mg/day
-2	75 mg/day
	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 2.

Toxicity	**Management/Next Dose for 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.

Toxicity	Management/Next Dose for Palbociclib
Grade 3 neutropenia (ANC<1000/mm3) **associated with a documented infection or fever >38.5° C,100.4° F**	• Hold drug. If ANC recovers (ANC ≥ 1000) within 2 weeks, resume drug and decrease drug by 1 dose level. • If ANC takes longer than 2 weeks to recover (ANC ≥1000), but within 3 weeks, then resume drug and decrease drug by 2 dose levels. • 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)	• First occurrence: 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 plt > 100,000, then resume drug and decrease by 1 dose level. • Recurrent Grade 3 thrombocytopenia: hold drug until plt >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. • If toxicity takes longer than 2 weeks to recover to < Grade 1, but within 3 weeks, then resume drug and decrease drug by 2 dose levels. • 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.
LFTs SGPT/ALT > 3X ULN SGPT/ALT and 2X ULN total bilirubin	Discontinue study treatment permanently.

QTc prolongation management

In the event of QTc prolongation, possible alternative reversible causes such as serum electrolytes 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 (see Appendix B).

Recommended dose modifications in the event of QTc prolongation are provided in the Table below.

Palbociclib Dose Modifications in the Event of QTc Prolongation

	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 life threatening 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 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.

If the QTc remains at >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 monitor.

6.2.4 Bazedoxifene dose modifications/delays

No dose reduction for bazedoxifene is permitted, but dosing interruptions are allowed. If bazedoxifene -related adverse events occur, they should be managed using standard clinical practice (e.g. hot flashes can be treated with venlafaxine).

If grade 3 or 4 toxicity occurs that the treating investigator feels is related to bazedoxifene, the study Principal Investigator should be contacted to discuss the case and determine whether continuation of protocol therapy is appropriate.

Treatment interruptions for up to 3 cumulative weeks for bazedoxifene therapy-related toxicities or personal reasons are allowed as per the investigator's best medical judgment. Palbociclib should not be held during bazedoxifene therapy interruption, unless palbociclib is on hold for a separate reason as described in section

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 Adverse Events Lists

7.1.1 Expected Toxicities for Palbociclib

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

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

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

7.1.2 Expected Toxicities for Bazedoxifene

In the two large randomized studies with bazedoxifene in healthy women the most common side effects were: hot flashes (20-24% of patients) and muscle cramps (12%). Most cases of hot flashes were mild to moderate and did lead to participant discontinuation from study. There were no safety concerns related to the cardiovascular system. The number of thromboembolic events was low (<1%) in the bazedoxifene treatment arms. There was one death in the bazedoxifene 40 mg group, a subject who experienced a prolonged air flight 30 days after study completion, was considered by the investigator to be possibly related to treatment.

In the dose escalation study 3 patients (including a patient on the bazedoxifene 5mg dose, 80mg dose and placebo) had asymptomatic elevations of ALT levels. In all cases LFTs declined after discontinuation of the study drug.

7.2 Adverse Event Characteristics

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

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

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

7.3 Expedited Adverse Event Reporting to DF/HCC

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

7.3.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4 Expedited Reporting to Pfizer

Within 24 business hours of first awareness of the event (immediately if the event is fatal or life threatening), the Overall PI will report to Pfizer by facsimile or email any Serious Adverse Event ("SAE," as defined below) for which reporting is required under this provision (as described below). Such SAEs are to be reported for study subjects or individuals otherwise exposed to the Pfizer Product as described below. The Overall PI should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available.

Principal Investigators will report SAEs using Form FDA 3500A (MedWatch). The Reportable Event Fax Cover Sheet provided by Pfizer must also be included with each SAE submitted (Appendix H).

7.4.1 SAE Definition for Reporting to Pfizer

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

7.4.2 Exposure During Pregnancy, Exposure During Lactation, Occupational Exposure

Even though there may not be an associated SAE, exposure to the Palbociclib and/or bazedoxifene during pregnancy, exposure to the Palbociclib and/or during lactation, and occupational exposure to the Palbociclib are reportable to Pfizer.

7.4.3 Hy's Law Cases

Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable to Pfizer. If a participant develops abnormal values in aspartate transaminase (AST) or alanine transaminase or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case.

7.4.4 SAE Reporting Period

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

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Expedited Reporting to Hospital Risk Management

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

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 Palbociclib

8.1.1 Description

Chemical name: 6-acetyl-8-cyclopentyl-5-methyl-2-(5-(piperazin-1-yl)pyridin-2-ylamino) pyrido[2,3-d]pyrimidin-7(8H)-one.
Chemical formula: C24H29N7O2
Molecular weight: 447.54.

Half life: ~29 hours.
Plasma protein binding of palbociclib: ~85%
Plasma protein binding of PF-05089326 (the lactam of palbociclib, one of the main metabolites present in plasma): 95%

Palbociclib (IC_{50} = 11 nM; Ki = 2 nM) is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, Palbociclib is primarily metabolized by CYP3A4 and SULT2A1 enzymes. Information on potential drug interactions can be found in section 5.4.

8.1.2 Form

Palbociclib will be supplied by Pfizer as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. Pfizer will supply the oral drug formulation to sites in High Density Polyethylene (HDPE) bottles containing 75 mg, 100 mg, or 125 mg capsules. The capsules can be differentiated by their size and color (see below).

Table 4. Palbociclib Capsule characteristics

Dosage	Capsule Color	Capsule Size
75mg	Sunset Yellow	2
100mg	Caramel/Sunset Yellow	1
125mg	Caramel	0

8.1.3 Storage and Stability

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

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

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

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

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

8.1.4 Compatibility

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

8.1.5 Handling

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

8.1.6 Availability

Palbociclib will be provided from the commercial supply and will be supplied free-of-charge from Pfizer.

8.1.7 Administration

Palbociclib will be provided in non-patient-specific bottles containing either 75 mg, 100 mg or 125 mg capsules.

The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Unused returned medication MUST NOT be re-dispensed to patients.

Palbociclib is an agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Only a single capsule strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously dispensed medication to the clinic and new capsules will be dispensed.

8.1.8 Ordering

Qualified personnel at participating sites will order the drug directly from Pfizer. The Drug Supply Request Form is in Appendix F.

8.1.9 Accountability

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

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

8.1.10 Destruction and Return

Sites will document and destroy unused investigational product per their local policies. The site primary investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

8.2 Bazedoxifene

8.2.1 Description

Chemical name: Chemical name: 1-{p-[2-(Hexahydro-1H-axepin-1-yl)ethoxy]benzyl}H-2-(p-hydroxyphenyl)-3-methylindol-5-ol monoacetate
Chemical formula: C3OH34N2O3,C2H4O2
Molecular weight: 530.7
Half life: ~30 hours.
Plasma protein binding of bazedoxifene : 98%-99%
Palbociclib (IC_{50} = 26 nM; Ki = 0.1 nM [ERα])
Bazedoxifene is absorbed from the gastrointestinal tract, with peak plasma concentrations occurring after about 2 hours. Bazedoxifene is absorbed from the gastrointestinal tract, with peak plasma concentrations occurring after about 2 hours. Bazedoxifene-5-glucuronide is the major circulating metabolite. It is expected to undergo enterohepatic recycling. Information on potential drug interactions can be found in section 5.4.

8.2.2 Form

Bazedoxifene will be supplied by Pfizer as tablets containing 20mg.

8.2.3 Storage and Stability

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

Bazedoxifene should be stored at 20-25°C (68-77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) in their original container.

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

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

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

8.2.4 Availability

Bazedoxifene is approved in the European Union for the treatment of post-menopausal osteoporosis in women at increased risk of fracture. It is an investigational agent for the treatment of breast and will be supplied free-of-charge from Pfizer.

8.2.5 Administration

Bazedoxifene will be provided in 4 x 7 count blister cards (28 tablets per carton) containing 20mg tablets.

The patient number should be recorded on the carton label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty blister cards should be returned to the site at the next study visit. Unused returned medication MUST NOT be re-dispensed to patients.

8.2.6 Ordering

Qualified personnel at participating sites will order the drug directly from Pfizer. The Drug Supply Request Form is in Appendix F.

8.2.7 Accountability

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

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

8.2.8 Destruction and Return

Sites will document and destroy unused investigational product per their local policies. The site primary investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The correlative studies are designed to be hypothesis generating. It is anticipated that promising findings will be validated in the context of future studies.

9.1 Research Tissue Specimen Collection

9.1.1 Tumor tissue will be collected at the following time points on this study:

- When available archival FFPE tissue samples of primary and/or metastatic disease will be retrieved preferably within 2 weeks of patient enrollment. Patients who do not have archival FFPE tissue samples available will not be required to have a biopsy.
- Baseline research biopsy to be done up to 2 weeks prior to starting treatment drug: Required in patients with easily accessible or accessible disease, as defined in Section 3.1.14
- Cycle 1 Day 15 (can be done within a window of +/- 3days) research biopsy: Optional in patients with easily accessible disease and accessible disease, as defined in Section 3.1.14
- Off-study research biopsy to be performed up to 4 weeks after disease progression has been determined: Required for patients with easily accessible and optional in patients with accessible disease, as defined in Section 3.1.14

Tissue specimens will be collected from tumor lesions using standard institutional procedures. For biopsies through the Brigham & Women's Hospital interventional radiology service, see Appendix E for standard operating procedures, amount of tissue to be collected, and processing instructions. If a patient has more than one site of disease, only one site needs to be biopsied, and the site is left to the discretion of the patient and her treating physician. Core biopsies are required and fine needle aspirates cannot be used. Patients who undergo an attempted research biopsy procedure for the purpose of this protocol, and in whom inadequate tissue is obtained, are not required to undergo a repeat biopsy in order to continue on protocol.

See Appendix E for additional details regarding research biopsies and processing guidelines.

9.2 Blood Sample Collection

Blood will be collected for cell-free DNA at baseline and on Day 1 of each cycle. The samples will be transferred to the Translational Research Lab, Belfor Institute, for isolation of cell free DNA and droplet digital PCR for the detection of *ESR1, PIK3CA, GATA3, FOXA1* and *NCOR1* mutations. Refer to Appendix E for specimen collection and shipping instructions.

An additional blood sample will be collected for germline DNA at baseline. If for any reason this sample is not collected at baseline, it can be collected at another time point during the study. The blood will be used for DNA isolation from white blood cells. Refer to Appendix E for specimen collection and shipping instructions

9.3 Drug Adherence

Drug diaries (Appendix D) will be maintained for patients to capture adherence to oral palbociclib and bazedoxifene therapy. Diaries will be completed prior to each protocol visit and reviewed for accuracy with the patient at each visit. Pill counts will be performed and recorded at each study visit by research staff. Optimal adherence is defined as >80% of medication taken. Patients found to be non-adherent with their medications will receive additional interventions by the treatment team to improve adherence (ie RN phone calls, extra visits as needed). If a patient demonstrates persistent non-adherence, their provider may remove them from the trial (as described in Section 5.5).

10. STUDY CALENDAR

All subjects must sign an informed consent document prior to initiation of any study related procedures. The consenting individual for the clinical trial must be an MD listed as a co-investigator on the trial.

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans must be done

≤4 weeks prior to the start of therapy.

Patients must meet all eligibility requirements prior to research biopsy (when applicable), as outlined in the eligibility criterion 3.1.14.

All assessments must be performed prior to administration of any study medication. Day 15 study assessments should be performed within ± 3 days of the protocol-specified date, unless otherwise noted. Day 1 study assessments for Cycle 2 and beyond should be performed within ± 3 days of the protocol-specified date. Restaging CT or MRI scans and bone scans may be done ± 7 days of the protocol-specified date, though it is preferred that they occur within the ±3 day window if possible.

After patients are taken off protocol treatment, they should be followed for survival every 4 months for up to 2 years or until time of death, whichever comes first. If a patient is taken off protocol treatment for any reason other than progression or death, then the patient should also be followed for progression with staging scans every 8 weeks until disease progression, start of alternative anti- cancer therapy, death, or withdrawal of consent, whichever comes first. These patients should also be followed for survival every 4 months for up to 2 years or until time of death, whichever comes first.

	Pre-Study -14 to 0 days	**C1 D1**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**D1 of each cycle**	**Every 2 cycles**	**At time of progression or off treatment**
Informed consent	X									
Demographics	X									
Medical history	X									
Physical exam	X	X[a]		X		X		X		X
Vital signs[b]	X	X[a]		X		X		X		X
Height	X									
Weight	X	X[a]		X		X		X		X
ECOG Performance status[c]	X	X[a]		X		X		X		X
CBC w/diff[d]	X	X[a]	X	X	X	X	X	X		X
Serum chemistry[e]	X	X[a]		X		X		X		X
PT,PTT[f]	X		X[f]							X[f]
CEA, CA27-29	X			X					X	
12-lead EKG	X			X		X			X	
FSH and estradiol[g]	X									
Serum/Urine Pregnancy Test B-HCG[h]	X									
Concomitant medication	X	X		X		X		X		
Perform pill count				X		X		X		X
AE evaluation	X			X		X		X		X
Tumor measurements[i]	X			X					X[j]	
Bone scan[k]	X									
Research biopsy[l]	X		X[l]							X[l]

Research blood sample	X[m]			X		X		X		X
Archival tissue[n]		X								
Survival Follow-up										X[o]

a. If performed at baseline ≤ 7 days of C1D1, procedure does not need to be repeated. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.
b. Vital signs: heart rate, blood pressure, respiratory rate
c. See Appendix A for ECOG PS guidelines
d. CBCs drawn on D15 can be drawn at a local lab. Lab results are then submitted to study team.
e. Serum chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose (random), total bilirubin, alkaline phosphatase, ALT, AST, albumin, calcium, magnesium, phosphorus.
f. PT, PTT if clinically indicated prior to biopsy (-ies) per standard institutional guidelines
g. Only applicable for screening, not for subsequent cycle visits, for women age <60 who have had amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression)
h. In women of childbearing potential only (including premenopausal women with intact uterus and ovaries on GnRH agonist).
i. Baseline tumor assessments should be performed ≤4 weeks prior to the start of therapy. Radiologic imaging studies to evaluate tumor status should be done every 2 cycles +/- 7 days. Contrast computed tomography (CT) (or without contrast if contraindicated) of chest and abdomen is preferred. Magnetic resonance imaging (MRI) of chest and abdomen is an acceptable alternative. Note: PET-CT scans are not allowed per protocol for primary assessment of response. PET-CT scans may be done according to clinical judgment to supplement CT or MRI scans in cases where results of the PET-CT may clarify or resolve a clinical question. If palpable/visible lesions (e.g. chest wall nodule, etc) is being used as a target lesions, measurements and photographs should be taken as well.
j. After C6, tumor measurements will be performed every 3 cycles.
k. A whole body bone scan should be acquired at baseline for all subjects ≤4 weeks prior to the start of therapy. For patients with measurable disease, skeletal lesions identified on the whole body bone scan at baseline, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan should be imaged at baseline and followed using localized CT, MRI or x-ray. Whole body bone scans need not be repeated after baseline unless clinically indicated. For patients with bone only disease, whole body scans will be performed every 6 months to confirm response, or earlier if clinically indicated. See 11.3.2.
l. Baseline research biopsy is required for patients with “easily accessible disease” and “accessible disease” (defined in section 3.1.14). Cycle 1 day 15 research biopsy is optional for patients with “easily accessible disease” and “accessible disease”. Off-treatment biopsy is required for patients with “easily accessible disease” and is optional for patients with “accessible disease”.
m. At the pre-study phase, samples will be collected for cell-free DNA and germline DNA. At Day 1 of cycle 2 and beyond, sample for cell-free DNA will be collected. Refer to Appendix E for further details.
n. Archival tissue can be collected at any time point throughout the study.
o. Follow-up every 4 months or until death

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 2 cycles (1 cycle = 4 weeks). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response. After cycle 6, tumor measurements will be performed every 3 cycles.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Objective response. Only those participants 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 target disease response. These participants will have their response classified according to the definitions stated below. Bone only disease, if there are lytic lesions, is also allowed and treatment response will be evaluated based on the MD Anderson criteria. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Evaluable for PFS. All participants randomized on this study are considered to be evaluable for PFS (whether or not they are eligible, have measurable disease, or receive protocol therapy).

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. These lesions will be evaluated by the RECIST 1.1 criteria. Lytic bone lesions or mixed lytic-blastic lesions that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions and response will be evaluated using the MD Anderson (MDA criteria) [34]. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks before the beginning of the treatment.

The same method of assessment and the same technique should 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 anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to

tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (L.K. Shankar, J.M. Hoffman, S. Bacharach, M.M. Graham, J. Karp, A.A. Lammertsma, S. Larson, D.A. Mankoff, B.A. Siegel, A. Van den Abbeele, J. Yap, D. Sullivan. Consensus recommendations for the use of 18F- FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med, 47(6):901-903, 2006). Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized. *In this protocol, PET or PET/CT should NOT be used as the primary modality to evaluate objective response, but may be used in an adjunctive fashion together with either CT or MRI in cases of uncertainty, as clinically indicated.*

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained. *In this protocol, endoscopy or laparoscopy will not be used for evaluation of response.*

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Cytology, Histology. 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).
The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Evaluation of Lytic Bone Lesion Target Lesion (MDA criteria)

Response category	**Criteria**
Complete response	Complete sclerotic fill-in of lytic lesions on x-ray or CT scan. Normalization of bone density on x-ray or CT scan. Normalization of signal intensity on MRI. Normalization of tracer uptake on skeletal scintigraphy
Partial Response	Development of a sclerotic rim or partial sclerotic fill-in of lytic lesions on x-ray or CT scan. Osteoblastic flare - Interval visualization of lesions with sclerotic rims or new sclerotic lesions in the setting of other signs of PR and absence of progressive bony disease. ≥ 50% decrease in measurable lesions on x-ray, CT, or MRI. ≥ 50% subjective decrease in the size of ill-defined lesions on x-ray, CT, or MRI. ≥ 50% subjective decrease in tracer uptake on skeletal scintigraphy.
Progressive Response	≥ 25% increase in size of measurable lesions on x-ray, CT, or MRI. ≥ 25% subjective increase in the size of ill-defined lesions on x-ray, CT, or MRI. ≥ 25% subjective increase in tracer uptake on skeletal scintigraphy. New bone metastases.

Stable Disease	No change < 25% increase or < 50% decrease in size of measurable lesions < 25% subjective increase or < 50% subjective decrease in size of ill-defined lesions No new bone metastases

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
*Measurements are based on the sum of a perpendicular, bidimensional measurement of the greatest diameters of each individual lesion.

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).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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* (new lesions must be > slice thickness) and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Note: If tumor response data is missing for target lesions, the overall assessment must be Unknown (UN) unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

Overall level of substantial worsening that merits discontinuation of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Evaluation of New Lesions

Definition of New Lesion: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

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.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

11.1.5 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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, including the baseline measurements.

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.7 Response Review

All staging studies will be reviewed centrally by the Dana-Farber/Harvard Cancer Center Tumor Imaging Metrics Core (TIMC).

11.1.8 Clinical Benefit

Clinical benefit will be defined as confirmed CR plus confirmed PR plus stable disease of at least 24 weeks duration.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

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

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Collaborative Agreements Language

Not Applicable.

13. STATISTICAL CONSIDERATIONS

This is a non-randomized, open-label, phase II study designed to evaluate the safety and efficacy of palbociclib, an oral selective CDK 4/6 inhibitor in combination with bazedoxifene, a third generation selective estrogen receptor modulator (SERM) in patients with metastatic hormone receptor positive breast cancer. Eligible participants must have histologically confirmed invasive breast cancer that is metastatic or unresectable locally advanced, and the breast cancer must be ER+/PR+, HER2- and endocrine resistant, and may have received up to one prior line of chemotherapy for metastatic or unresectable locally advanced breast cancer.

13.1 Study Design/Endpoints

Primary endpoint:

- Clinical benefit rate (CR + PR + SD $\geq$ 24 weeks)

Secondary endpoints include:

- Safety and toxicity profile
- To evaluate objective response by RECIST 1.1.
- Progression-free survival
- Overall survival
- Objective response, clinical benefit rate, progression free survival and overall survival for patients with ESR1 mutations.

Statistical programming and analyses will be performed using SAS and other validated statistical software as required.

This study uses a Simon 'optimal' two-stage design, 17 patients will be enrolled in the first stage, and if the study continues to the second stage, another 20 patients would be enrolled. A total of 37 patients will be enrolled in this study. If a dose de-escalation is performed, the patients that received the initial palbociclib dose, will not be evaluated for efficacy and the maximum number of patients in this study will be 43 patients.

There are no phase I data with the combination of palbociclib and bazedoxifene. Based upon the observed toxicities to date, mechanism of action, and drug metabolism, no additive or synergistic toxicities are anticipated. Accrual will be paused and a formal monitoring of safety will be conducted when 6 patients have completed at least 1 cycle of treatment to determine if any toxicities requiring a dose de-escalation is needed. If >1 patient develops a dose limiting toxicity, a dose de-escalation to dose level -1 (100mg) will be performed and a formal monitoring of safety will be performed when 6 patients have completed at least 1 cycle of level -1 dose. If >1 patient develops a dose limiting toxicity with level -1 dose, the study will be discontinued. The following table gives the probability of continuing after 6 patients under varying true rates of dose-limiting toxicity.

	Acceptable dosage using 6 subjects						
True DLT rate	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**
Probability	89%	66%	42%	23%	11%	4%	1%

Accrual will be paused after the 17 patients are enrolled until at least 4 patients demonstrate clinical benefit at 6 months (24 weeks) and all patients complete at least 2 cycles for safety evaluation. The length of the pause will range from 2 cycles to 6 months. If 8 or more patients among the 17 patients enrolled in the first stage of the Phase II experience a DLT, the regimen will be considered too toxic and the study will be closed due to safety concern. . If 7 or less of 17 patients experience a DLT, continued enrollment to the second stage will be based on the Simon two-stage design to evaluate clinical benefit. Assuming that the true rate of adverse events is 30%, the probability that 8 or more patients experience DLT is 10%. Assuming an unacceptable adverse event rate of 60%, there is a 91% probability of observing 8 or more events and stopping due to a safety concern.

DLT is based on the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) and will be assessed over the first two cycles of treatment. A DLT will be defined as follows:

- Grade 3 or higher hematologic or non-hematologic toxicity thought likely or definitely related to protocol therapy will be counted as a DLT, *with the exception* of:

    - Grade 3 neutropenia without fever
    - Grade 3 diarrhea that responds to maximal supportive measures. If grade 3 diarrhea is persistent > 7 days despite maximal supportive measures, it will be counted as a DLT
    - Grade 3 fatigue
    - Grade 3 hot flashes
    - Grade 3 electrolyte disturbance, unless persistent > 7 days despite maximal supportive measure

Patients who withdraw study consent before receiving any study treatment will be replaced. Patients who develop inevaluable disease during treatment or off study before follow-up disease evaluation would be considered as non-responders in final analyses.

13.2 Sample Size, Accrual Rate and Study Duration

A true clinical benefit rate of 20% or less would not be of clinical interest, and is the null hypothesis to the Simon two-stage design. A true rate of 40% among patients with ER/PR+, HER2-, endocrine resistant metastatic or unresectable locally advanced breast cancer would be considered a clinically meaningful level of response, so the sample size was chosen to have high power (90%) to declare the combination effective at this rate, while controlling the one-sided Type I error at no more than 10% under the null.

Using the Simons optimal method, in the first stage, 17 patients will be enrolled. If there are at least 4 responses, accrual will continue to the second stage where up to 20 additional patients will be enrolled. If at least 11 of these 37 patients have response (≥30%), the regimen will be considered worthy of further study. With this design, the probability of stopping the trial early is 55% if the true response rate is 20%. If the true response rate is 40% the chance that the regimen is declared worthy of further study is 90%.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	3	+	0	=	3
Not Hispanic or Latino	34	+	0	=	34
Ethnic Category: Total of all subjects	37	+	0	=	37
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	3	+	0	=	4
Black or African American	3	+	0	=	4
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	31	+	0	=	31
Racial Category: Total of all subjects	37	+	0	=	37

13.3 Analysis of Primary Endpoints

The primary endpoint is clinical benefit at 24 weeks. Patients who received at least one dose of the study regimens will be included in the assessment of objective response. Assuming the study does not terminate early and all patients enrolled begin protocol therapy, the 95% CI for the response rate will be determined accounting for the two-stage design.

13.4 Analysis of Secondary Endpoints

All patients who receive at least one dose of the study regimens will be included in the assessment of safety and toxicity.

Adverse event information will be collected from the time the subject signs the ICF until resolution or for 30 days after the subject's last study visit, whichever comes first. Treatment-emergent AEs (TEAEs) will be analyzed. Adverse events will be regarded as TEAEs if they started on or after the date and time of administration of the first dose of study treatment or if they were present before the administration of the first dose of study treatment and increased in severity during the study. Treatment-emergent peripheral neuropathy will be followed until resolution or until the start of another anticancer therapy post treatment, whichever occurs first.

Adverse events will be graded using CTCAE v 4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Investigators will collect all CTCAE grades for all AEs (to assess both increasing and decreasing severity). Events will be summarized by frequency and percentage by grade and by type.

The incidence of TEAEs and relatedness to study treatment will be summarized.

Objective response rate will be calculated and the 95% CI for the response rate will be determined accounting for the two-stage design.

Progression-free survival and Overall survival, as defined in section 11.1.6, will be described using the method of Kaplan-Meier. The point estimate of median PFS and OS, as well as estimates of PFS and OS at other time points, will be presented with 95% confidence intervals.

It is anticipated that 20% of patients will have detectable *ESR1* mutations. Assuming a 40% clinical benefit rate and a 20% ESR1 mutation rate, we have 80% power to detect the difference of clinical benefit rates between patients with and without ESR1 mutation if the clinical benefit rate is 80% among patients with *ESR1* mutation and 30% among patients without *ESR1* mutation. The following table gives the power of detecting the clinical benefit rate difference among patients with and without ESR1 mutation, assuming the total sample size is 37 and clinical benefit rate is 40%.

ESR1 mutation rate	# of pts with ESR1 mutation	# of pts without ESR1 mutation	CBR among pts with ESR1 mutation	CBR among pts without ESR1 mutation	Power
20%	7	30	80%	30%	82%
	7	30	75%	33%	70%
	7	30	70%	31%	57%
25%	9	28	80%	27%	92%
	9	28	75%	28%	82%
	9	28	70%	30%	69%
30%	11	26	80%	23%	97%
	11	26	75%	25%	91%
	11	26	70%	27%	80%

Other analyses for correlative objectives are exploratory with no plans for formal hypothesis testing given the limited sample size.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All participants who have received at least one dose of study regimens will be evaluable for toxicity.

13.5.2 Evaluation of Response

All participants who have received at least one dose of study regimens will be evaluable for response. Patients who develop inevaluable disease during treatment or off study before follow-up disease evaluation would be considered as non-responders in final analyses.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B LIST OF DRUGS KNOWN TO PREDISPOSE TO TORSADE DE POINTES

Generic Name	Brand Name
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	V ascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S.®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

APPENDIX C CYP3A INDUCERS/INHIBITORS AND INFORMATION ON POSSIBLE DRUG INTERACTIONS

Medications that strongly inhibit CYP3A:
Amprenavir
Atazanavir
Boceprevir
Clarithromycin
Conivaptan
Delavirdine
Diltiazem
Erythromycin
Fosamprenavir
Indinavir
Itraconazole
Ketoconazole
Lopinavir
Mibefradil
Miconazole
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Verapamil
Voriconazole
Grapefruit, grapefruit juice, or any product containing grapefruit

Medications that strongly induce CYP3A:
Carbamazepine
Felbamate
Nevirapine

Phenytoin
Primidone
Rifabutin
Rifampicin
Rifampin
Rifapentin
St. John's wort

Medications that moderately induce CYP3A:
Bosentan
Efavirenz
Etravine
Modafinil
Nafcillin

APPENDIX D STUDY PARTICIPANT SELF-ADMINISTERED DRUG DIARY

PATIENT INSTRUCTIONS:

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

For Palbociclib:

- Keep Palbociclib capsules in the bottle(s) provided and do not transfer them to any other container. Store at room temperature.
- Palbociclib should be taken by mouth once per day. Palbociclib should be taken with food. Grapefruit, grapefruit juice or anything that contains grapefruit juice and St. John's wort must be avoided while on study.
- Capsules must be swallowed whole. Do not soak capsules or empty contents into any food or drink.
- If you vomit after taking Palbociclib, do NOT take another dose. Please note any vomiting in the **Comments** section of the diary on the next page.
- If a dose is missed and it is less than 6 hours from usual time of dosing, then you may take that dose. Otherwise that dose should be skipped and NOT taken. You should resume regular dosing the following day. If you miss a dose, record "0" for Number Taken on the next page.
- If you accidentally take an extra dose during a day skip the next day's dose and record the extra dose on the next page.

For Bazedoxifene:

- Keep Bazedoxifene tablets in the blister card(s)provided and do not transfer them to any other container. Store at room temperature.
- Bazedoxifene should be taken by mouth once per day. Bazedoxifene can be taken with or without food.
- If you vomit after taking Bazedoxifene, do NOT take another dose. Please note any vomiting in the **Comments** section of the diary on the next page.
- If a dose is missed and it is less than 6 hours from usual time of dosing, then you may take that dose. Otherwise that dose should be skipped and NOT taken. You should resume regular dosing the following day. If you miss a dose, record "0" for Number Taken on the next page.
- If you accidentally take an extra dose during a day skip the next day's dose and record the extra dose on the next page.

<table>
<tr><th colspan="3">FOR CLINIC USE ONLY:</th></tr>
<tr><td rowspan="7">Give patient all 3 pages of Drug Diary stapled together. Provide one diary per cycle (28 days).

Complete patient identifiers and medical team contact information on pages 2 and 3.

Complete correct dose levels for Palbociclib and Bazedoxifene treatment on page 2.

When patient returns pill bottles/blister cards and diary perform a Palbociclib and Bazedoxifene pill count and record adherence information in the box to the right.</td><td colspan="2">Staff Initials:</td></tr>
<tr><td>Date Dispensed:</td><td>Date Returned:</td></tr>
<tr><td># Palbociclib capsules dispensed:</td><td># Palbociclib capsules returned:</td></tr>
<tr><td colspan="2"># Palbociclib capsules that should have been taken:</td></tr>
<tr><td># Bazedoxifene tablets dispensed</td><td># Bazedoxifene tablets returned:</td></tr>
<tr><td colspan="2"># Bazedoxifene tablets that should have been taken:</td></tr>
<tr><td colspan="2">Discrepancy Notes:</td></tr>
</table>

15-060 STUDY PARTICIPANT SELF-ADMINISTERED DIARY

Participant Name: _____ Cycle #: _____

Your Doctor: _____ Phone: _____

Your Nurse: _____ Phone: _____

PALBOCICLIB

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

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

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

Patient Signature: _____ Date: _____/_____/_____

15-060 STUDY PARTICIPANT SELF-ADMINISTERED DIARY

Participant Name: _____ Cycle #: _____

BAZEDOXIFENE

STUDY DRUG INSTRUCTIONS: Take two Bazedoxifene 20mg tablets on Days 1 – 28. Record the dose of each medication on the chart to the right after taking each day.

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

Patient Signature: _____ Date: _____/_____/_____

APPENDIX E RESEARCH SPECIMEN COLLECTION/SHIPPING GUIDELINES

Research Biopsy Guidelines

Tissue specimens will be collected from recurrent or metastatic lesions using standard institutional procedures. The amount of tissue collected will follow the guidelines listed below:

- *Breast:* A goal of 3-6 core biopsy specimens will be obtained using standard institutional guidelines for a diagnostic core biopsy of a breast mass.

- *Skin/chest wall:* A goal of 1-2 5-mm punch biopsies will be obtained.

- *Lymph node:* A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle.

- *Liver:* A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle.

- *Lung:* Because of the risk of pneumothorax associated with core needle biopsies of lung nodules, no core biopsies of lung nodules will be performed on this protocol; unless if they are clinically indicated.

- *Bone:* Because the yield of malignant tissue from bone biopsies tends to be relatively low, if a patient has another accessible site of disease (i.e. skin, lymph node, liver), that site should be biopsied preferentially. If bone is the only biopsy-accessible site, then a goal of 3-6 core biopsy specimens will be obtained using an 11-13 gauge needle.

- *Pleural Fluid:* A goal of 500 cc of pleural fluid will be obtained with a standard thoracentesis procedure, with or without image guidance, according to the clinical judgment of the treating physician and clinician performing the procedure. Less than the goal amount is acceptable, and should be based upon the clinical judgment of the Investigator and the clinician performing the procedure. If more than the goal amount of fluid is obtained, then the entire specimen (with the exception of what is needed for clinical purposes, if applicable) will be stored in the tissue bank.

- *Ascites fluid:* A goal of 500 cc of ascites fluid will be obtained with a standard paracentesis procedure, with or without image guidance, according to the clinical judgment of the treating physician and clinician performing the procedure. Less than the goal amount is acceptable, and should be based upon the clinical judgment of the Investigator and the clinician performing the procedure. If more than the goal amount of fluid is obtained, then the entire specimen (with the exception of what is needed for clinical purposes, if applicable) will be stored in the tissue bank.

Please note that the above are guidelines for the amount of tissue to be obtained, and are not meant to replace clinical judgment at the time the procedure is performed. Less than the goal quantity of tissue is accepted for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure. If ascites or pleural fluid is to be used as the investigational biopsy specimen, consideration should be given to confirming the malignant nature of the ascites or pleural fluid prior to study entry.

If a patient is undergoing resection of a lesion for clinical reasons (i.e. wedge resection of a new lung lesion for confirmation of diagnosis or re-testing of hormone receptor or HER2 status; or, resection of a chest wall lesion; or, resection of a lymph node), then the patient may opt to have a portion of that tissue (roughly equivalent to the goal amount of tissue listed in the guidelines above, i.e. the equivalent of two 5-mm punch biopsies of the skin, or 3-6 18-gauge core biopsies) stored for research at the time of the procedure (provided that the tissue is processed as specified in Section 8.3), in which case, the patient would not be required to undergo a separate research biopsy for entry into this protocol.

Tissue Biopsy Handling and Processing

Following research biopsy of a specimen, 1 tissue core will be placed in formalin and sent to SHL for embedding in paraffin. FFPE blocks will be sectioned and 20 slides will be cut for H+E and Immunohistochemistry staining that will be performed at the SHL core directed by Dr. Jon Aster. The other cores will be frozen in OCT and sent to the Broad Institute for the Center for Cancer Precision Medicine **(**CCPM) testing (whole exome sequencing and RNAseq). The remaining tissue will be stored for future research. All samples will be anonymized by assigning a unique sample ID number prior to use.

Archival Tissue Collection

Tissue blocks of primary and/or metastatic tumor samples should be sent to Dana- Farber Cancer Institute within in 2 weeks of the start of protocol therapy. If blocks cannot be submitted, 20 unstained slides are acceptable.

Cell free DNA (cfDNA) blood collection

Blood will be collected at baseline and on Day 1 of each cycle. One 10 ml of blood will be collected in EDTA containing tube at each time point. The samples will be sent to the DFCI breast blood bank and processed for cell free plasma. Samples will be sent to the Broad Institute for low passage sequencing to assess cell free DNA and samples that are found to have adequate tumor DNA will undergo whole exome sequencing. Analysis of the ESR1 mutations using droplet-digital PCR will also be performed at the Belfer Institute, DFCI.

Broad Institute
Contact: Megan Hana
Manager of Operations Cancer Center Genome Analysis
75 Ames St.
Cambridge, MA 02142

Belfer Institute
Contact: Cloud Paweletz Ph.D.
Harvard Institutes of Medicine
4 Blackfan St.
Boston, MA 02215

Germline DNA blood collection

One 10 ml EDTA tube will be collected for research at baseline and will be sent to the Broad Institute for the Center for Cancer Precision Medicine **(**CCPM) testing for germline DNA testing. If for any reason this sample is not collected at baseline, it can be collected at another time point during the study. Excess germline DNA will be returned to DF/HCC Clinical Trials Core laboratory.

APPENDIX F INVESTIGATOR-INITIATED RESEARCH DRUG SUPPLY REQUEST

CLINICAL AND MEDICAL CONTROLLED DOCUMENT (CMCD)
REQUIRED FORM – DRUG SUPPLY REQUEST FORM

IMPORTANT: It is recommended that the Principal Investigator maintain a drug inventory sufficient to treat study subjects for approximately **four (4) weeks** while waiting for additional ordered supplies. Please contact **at 212-733-1058 or Benedetta.Campanelli@pfizer.com** if you have questions regarding the expected timeframe for the initial and any subsequent shipments.

TO: Benedetta Campanell **FAX:** 646-348-8322 (for drug orders only)

CSDS PROTOCOL NUMBER

STUDY INFORMATION

PFIZER REFERENCE NUMBER	WI196579	INSTITUTION PROTOCOL	
PROTOCOL TITLE	A Phase II Study of Palbociclib in Combination with Bazedoxifene in Hormone Receptor Positive Breast Cancer		
PRINCIPAL INVESTIGATOR	Rinath Jeselsohn, MD		

ORDER INFORMATION

DATE ORDERED		IRB/IEC APPROVAL DATE	
INITIAL SHIPMENT?	☐ YES ☐ NO	DATE REQUIRED	

PRODUCT	STRENGTH	FORMULATION	NUMBER
PD-0332991(Palbociclib) (23 Per Bottle)	75mg	capsules	
PD-0332991(Palbociclib) (23 Per Bottle)	100mg	capsules	
PD-0332991(Palbociclib) (23 Per Bottle)	125mg	capsules	
Bazedoxifene (Blister cartons, 4/7 blisters 28 per carton)	20mg	tablets	

ADDITIONAL COMMENTS	Please do not order drug until patient has been fully screened.

CONTACT & SHIPPING INFORMATION

Please be sure that the most current SHIP TO information is listed, otherwise supplies may be delayed.

	CONTACT	SHIP TO	OTHER
NAME			
INSTITUTION			
MAILING ADDRESS			
TELEPHONE			
FAX			
EMAIL			

APPENDIX G PHARMACY RECOMMENDATIONS FOR DISPENSING PALBOCICLIB

For this trial Pfizer distributes Palbociclib in bottles containing 23 capsules. Participants should only take 21 capsules (Days 1-21 of each 28 day cycle). With approval from Pfizer and as a preventive measure and from participants taking all 23 capsules we are recommending that pharmacies remove the 2 extra capsules from each bottle before dispensing to the participants since Pfizer is unable to distribute bottles containing only 21 capsules. While this is not required we strongly recommend this procedure to prevent participants from taking extra capsules.

This process will require careful drug account ability documentation. On the DARF document that 21 capsules were dispensed to the participant. A second line should be recorded to state "Destroyed per SOP" in the patient initials and MRN fields and "-2" for the amount dispensed.

APPENDIX H REPORTABLE EVENT FAX COVER SHEET FOR REPORTING TO PFIZER

Pfizer	CT25-WI-GL03-RF06 3.0	REPORTABLE EVENT FAX COVER SHEET (US)	01-AUG-2014

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

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

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

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

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

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

TO: *Pfizer U.S. Clinical Trial Department*		
FAX: *1-866-997-8322*		
FROM:		DATE:
TELEPHONE:		FAX:
NUMBER OF PAGES (INCLUDING COVER SHEET):		
PRODUCT	Palbociclib, Bazedoxifene	
PFIZER REFERENCE NUMBER	WI196579	EXTERNAL REFERENCE NUMBER
STUDY TITLE	A Phase II Study of Palbociclib in Combination with Bazedoxifene in Hormone Receptor Positive Breast Cancer	
PATIENT NUMBER		
INVESTIGATOR	Rinath Jeselsohn, MD	