Local Protocol #: *13-559*

TITLE: A Phase 2 Pilot Feasibility Study of Palbociclib in Combination with Adjuvant Endocrine Therapy for Hormone Receptor Positive Invasive Breast Carcinoma

Coordinating Center: Dana-Farber Cancer Institute

***Principal Investigator (PI):** Erica L. Mayer, MD, MPH
Breast Oncology Center
Dana-Farber Cancer Institute
[redacted]

[redacted] **Investigators:**
[redacted]

Quality of Life Analysis:

[redacted]

[redacted]

Statistician:

William Barry, PhD
Department of Biostatistics and Computational Biology
Dana-Farber Cancer Institute

[redacted]

Project Manager:

[redacted]

Study Coordinator:

DFCI Study Coordinator
Dana-Farber Cancer Institute
Breast Oncology
450 Brookline Ave.
Boston, MA 02215

[redacted]

Responsible Research Nurse:

[redacted]

Industry (Pfizer)-Supplied Agent: Palbociclib
Other Agent(s): Aromatase inhibitor (letrozole, anastrozole, or exemestane), supplier: commercial. Tamoxifen, supplier: commercial.

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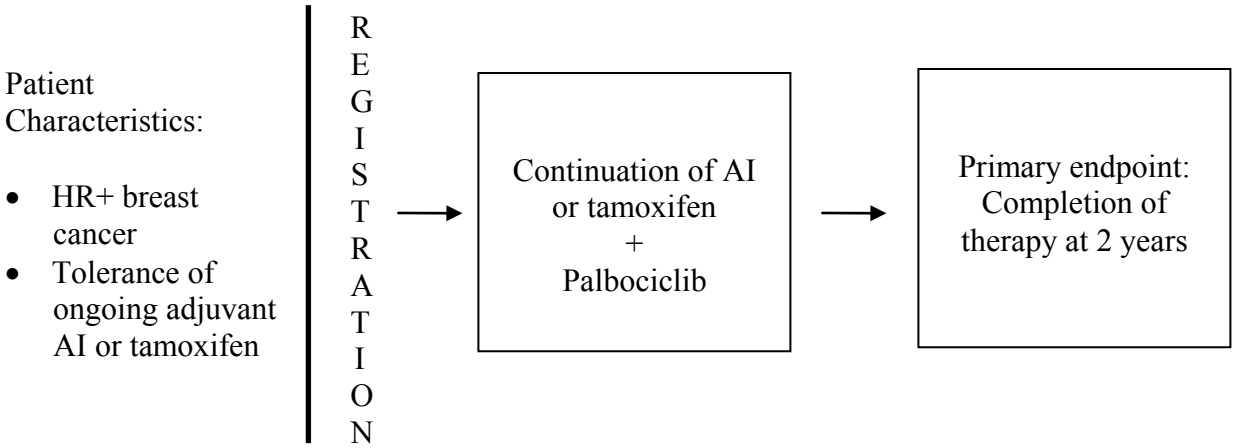
SCHEMA

Non-randomized phase II study
N = 165; Cycle = 28 days



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1. OBJECTIVES

1.1 Study Design

This is a single arm phase II pilot study designed to evaluate the feasibility of combining palbociclib with 2 years of adjuvant endocrine therapy (aromatase inhibitor (AI) or tamoxifen) for patients with hormone receptor positive (HR+) breast cancer.

1.2 Primary Objectives

To evaluate the treatment discontinuation rate at 2 years for patients receiving combination therapy with endocrine therapy plus palbociclib.

1.3 Secondary Objectives

- To evaluate treatment discontinuation rates in the subgroups of patients that receive AI and tamoxifen-based therapy

- To describe the safety of extended duration therapy with endocrine therapy plus palbociclib.

1.4 Correlative Objectives

- [redacted]
- [redacted]

2. BACKGROUND

2.1 Hormone Receptor Positive Breast Cancer

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

A variety of novel agents are in development to improve the efficacy of endocrine therapy against HR+ breast cancer. One pathway of interest is the PI3K/mTOR pathway, and agents targeting this pathway, including everolimus, have demonstrated efficacy in combination with either aromatase inhibitors or tamoxifen when treating endocrine-resistant metastatic HR+ breast cancer.[1,2] Cell cycle inhibition is another target of choice, forming the biological motivation for the proposed trial.

2.2 Palbociclib Mechanism of Action

Cell cycle inhibition is a target of choice for novel cancer therapeutics. PD-0332991 (palbociclib), an orally active pyridopyrimidine, is a potent first-in-class, highly selective reversible inhibitor of CDK 4 and CDK6 (IC_{50} = 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.[3-5] 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.[5] CDK activity and G1 progression is negatively regulated by Cip-Kip and INK4 family, typified by p16.[6-10] Overexpression of p16 in cells with normal Rb inhibits both CDK4-and CDK6-associated kinase activity and Rb phosphorylation, with subsequent cell cycle arrest.[11,12]

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.[13] Cyclin D1 is a direct transcriptional target of ER[14-17] and microinjection of antibodies to cyclin D1 inhibits estrogen-induced S-phase entry.[18-22] In addition, anti-estrogen-induced growth arrest of ER+ breast cancer cells is accompanied by decreased cyclin D1 expression[23] while endocrine resistance is associated with persistent cyclin D1 expression and Rb phosphorylation.[24] 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[25] and CDK4/6 inhibitors are most effective in tumors with gene amplification and overexpression of cyclin D1,[26-28] which is common in ER+ breast cancer. For example, palbociclib was most effective for ER+ breast cancer in a cell line panel,[29] including those that exhibited anti-estrogen resistance. Genetic aberrations leading to hyperactivation of cyclin D1-CDK4/6 is particularly common in ER+ breast cancer, consistent with its critical role in the tumorigenesis of this cancer subtype,[29] making CDK4/6 inhibitors particularly attractive agents for ER+ breast cancer.

2.3 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*[27] 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.[27]

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. Of note for 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+ human breast cancer cell lines indicating a synergistic interaction[29] and provided a biologic rationale for evaluating the combination of palbociclib with anti-hormonal therapy in the clinic. Also, most recent data from Julie Kan's group in hormone resistant models (MCF7-CYP19) indicate a significant benefit from the combination of palbociclib and letrozole as well as palbociclib and fulvestrant over single agent letrozole and fulvestrant (Pfizer, unpublished data).

Once daily oral administration of palbociclib was well tolerated in rats at levels of 10 mg/kg/day for males and up to 200 mg/kg/day for females (Sponsor Reference No. 12LJ025) [30].

Palbociclib has been evaluated in safety pharmacology, genetic toxicity, reproductive and development (fertility and early embryonic development, embryofetal development), and repeat-dose toxicity studies of up to 15-weeks duration in the rat and dog. Based on the nonclinical safety studies conducted with palbociclib, the primary palbociclib-related systemic toxicities were observed in hematolymphopoietic tissues (decreased cellularity, increased iron pigment, decreases in peripheral leukocytes and RBC parameters) and male reproductive organs (degeneration of seminiferous tubules, secondary epididymal hypospermia and increased intratubular cellular debris). Partial to complete reversibility of toxicities was demonstrated following a 4 week recovery period, with the exception of the male reproductive organ findings in the dog. These toxicities occurred in both rats and dogs, and are consistent with the intended pharmacologic effect of palbociclib (i.e., cell cycle inhibition). (Fink et al, 2001; Arguello et al, 1998; Bartkova et al, 2003). Palbociclib was also identified with the potential to cause QT prolongation, developmental effects, and aneugenicity. Developmental effects that were considered adverse included a decrease in fetal body weights in rats and a low incidence of small phalanges on the forepaws in rabbits. A

no effect level for aneugenicity was observed at approximately 7-fold higher than unbound systemic AUC24 exposures associated with the human clinical dose of 125 mg QD.

Palbociclib is being further evaluated for chronic toxicity in a 6-month rat and 9-month dog repeat-dose toxicity study. Cataracts have been identified in rats following 27-weeks of intermittent dosing. The minimal dose level for cataract formation has not been identified from the 27-week rat toxicity study, based on the histological data (lens degeneration was noted microscopically). Cataracts were identified from ophthalmic evaluations at the lower examined dose of 30 mg/kg/day in males but at no dose in females.

Further data from this toxicity study suggested a correlation between altered glucose metabolism and the formation of cataracts/lens degeneration. In dog toxicity studies (15-week and 39-week), no altered glucose levels or cataracts/lens degeneration have been observed (lack of lens degeneration not yet confirmed in the 39-week study; histopathology pending). Hyperglycemia and diabetes mellitus are not considered to be identified clinical risks and are not considered to be adverse drug reactions (ADRs) of palbociclib.

2.4 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 ($AUC_{(0-10)}$ and C_{max}) 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 Day 14 and Day 21 (assumed to be steady state), palbociclib was absorbed with a median T_{max} of ~4 hours. The mean palbociclib Vz/F was 3103 L, which is significantly greater than total body water (42 L), indicating that palbociclib extensively penetrates into peripheral tissues. Palbociclib was eliminated slowly; the mean elimination half-life ($t_{½}$) was 26.5 hours (ranged 15.8 to 36.2 hours) and the mean CL/F was 86.1 L/hour. Palbociclib accumulated following repeated dosing with a median R_{ac} of 2.4, which is consistent with the terminal half life.

A pilot food effect assessment was built into Protocol A5481001 and conducted in 12 patients following administration of either 125 mg or 200 mg doses (the maximum tolerated dose/recommended phase 2 dose (RP2D) for the 3/1 and 2/1 schedules, respectively). In general, no change in the rate of absorption was observed between the fed and fasted state (median T_{max} = 7 hours for both; range 3.5-23 hours). However, higher exposures and peak concentrations were observed in the fed state compared to the fasted state (mean $AUC_{(0-10)}$: 370.5 vs 290.5 ng•hr/mL, respectively; mean C_{max}: 59.7 vs 42.8 ng/mL, respectively). Based on these data, it can be concluded that since administration of palbociclib with a high fat meal may increase palbociclib exposure, patients should be fasted from 1 hour before to 2 hours after dosing (water is allowed), unless otherwise indicated in clinical protocols. The effect of a non-fat meal on the PK of palbociclib has not been evaluated.

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 Cytochrome P-450 (CYP) 3A4 enzymes. An exploratory evaluation of the circulating metabolites for palbociclib was conducted in plasma samples obtained from patients treated with palbociclib 200 mg QD (Schedule 2/1) in Study A5481001. Preliminary assessment of the pooled plasma samples on Day 14 of Cycle 1 indicated that the glucuronide conjugate of palbociclib and the lactam of palbociclib (PF-05089326) were the main metabolites present in plasma. Other metabolites observed were the glucuronide conjugates of hydroxylated palbociclib and the glucuronide conjugate of reduced palbociclib. PF-05089326 was also observed in the circulation of rats following repeated daily oral administration of palbociclib at the dose levels of 50 and 100 mg/kg/day. Plasma protein binding of palbociclib and PF-05089326 is ~85% and 95%, respectively.

2.5 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.

2.6 Palbociclib Clinical Data

2.6.1 Phase II palbociclib monotherapy study in advanced breast cancer

A phase II study is ongoing with single agent palbociclib in 36 women with advanced breast cancer. Preliminary results were reported at

the American Society of Clinical Oncology (ASCO) 2013 from 28 women who have completed cycle 1.[31] Palbociclib is given at 125 mg orally, days 1- 21 of a 28-day cycle. Of the 28 women, 18 women are (64%) 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%) pts for cytopenias; 27/28 patients discontinued study for disease progression. (PR + SD $\geq$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.

2.6.2 Phase I/II trial of palbociclib in combination with letrozole in advanced breast cancer

A randomized, multicenter active-controlled Phase 1/2 Study (A5481003) was designed to assess the efficacy, safety and PK of letrozole 2.5 mg QD (continuously) in combination with palbociclib 125 mg QD (schedule 3/1) versus single agent letrozole 2.5 mg QD (continuously) 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 was comprised of a limited Phase 1 portion, aimed at confirming the safety and tolerability of the combination and excluding a PK interaction with the combination, and a randomized Phase 2 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 2 portion 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[32] indicated no PK interaction between palbociclib and letrozole with mean $AUC_{(0-24)}$ of 2047 and 2021 ng•hr/mL (n=12) for palbociclib in the absence and presence of letrozole, respectively, and 2027 and 1776 ng•hr/mL (n=11) for letrozole in the absence and presence of palbociclib, respectively. The RP2D was determined to be 125 mg QD on Schedule 3/1 (3 weeks continuous treatment followed by 1 week 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 $\geq$ 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).[33]

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.

Updated Safety Analysis of Study A5481003

Cumulative incidences of the most relevant all causality, any Grade toxicities reported within the first year, and within the first 2 years of treatment with palbociclib were examined in 95 treated subjects enrolled in Study A5481003 with a data cutoff of 29 November 2013 (see table below). The cumulative incidence of neutropenia was identical (75.8%) within the first 2 years compared with within the first year of dosing, indicating that the hematologic effects of palbociclib tend to occur early during treatment and suggesting further that there is no evidence for long-term or cumulative toxicity with regard to palbociclib's myelosuppressive effects. The cumulative incidences of other reported hematologic events were only slightly increased within the first 2 years, as opposed to the first year of treatment only, including for Leucopenia (45.3% vs. 38.9%), Anemia (33.7 vs. 29.5%) and Thrombocytopenia (16.8% vs. 12.6%), yet the incidence was identical for Platelet count decreased (3.2% vs. 3.2%) and Hemoglobin decreased (3.2% vs. 3.2%). For gastrointestinal toxicities, the cumulative incidences were only marginally increased within the first 2 years of treatment with palbociclib, compared to the first year only: Nausea (28.4% vs. 26.3%), Vomiting (14.7% vs. 13.7%), Diarrhea (22.1% vs. 18.9%), and Constipation (13.7% vs. 9.5%). Similarly, only small numerical differences were observed in cumulative incidences within the first 2 years of treatment compared with treatment during the first year only with regard to adverse events indicating Mucositis, such as Mucosal inflammation (7.4% vs. 7.4%) and Stomatitis (11.6% vs. 7.4%), or with regard to infections, such as Nasopharyngitis (14.7% vs. 12.6%), Influenza (9.5% vs. 8.4%), Urinary tract infection (7.4% vs. 6.3%), and Influenza-like illness (5.3% vs. 5.3%). The corresponding incidence for hepatic (ALT increased, 6.3% vs. 5.3%; AST increased, 6.3% vs. 6.3%) or renal (Blood creatinine increased, 6.3% vs. 5.3%) laboratory parameters are similarly reassuring. The cumulative incidences of other commonly reported adverse events also remained relatively stable over time (ie, cumulative incidence

within the first 2 years of treatment with palbociclib compared with the cumulative incidence within the first year only), suggesting that currently there is no evidence to suspect any specific cumulative or long-term toxicity as a result of prolonged exposure to palbociclib: Fatigue (45.3% vs. 38.9%), Hot flush (21.1% vs. 21.1%), Alopecia (20.0% vs. 18.9%), Arthralgia (23.2% vs. 18.9%), and Asthenia (12.6% vs. 10.5%).

Cumulative Incidence of TEAEs (All Causality) in the First Year of Treatment, the First 2 Years of Treatment, and in those Subjects Treated for More Than 2 Years of With Palbociclib on Study A5481003 (Descending Order of Frequency for Events Reported at Incidences >10% in the First Year)

Adverse Events	First Year N = 95	First 2 Years N = 95	> 2 Years N = 29
Any adverse event	98.9	100.0	100.0
Neutropenia	75.8	75.8	82.8
Fatigue	38.9	45.3	55.2
Leukopenia	38.9	45.3	51.7
Anaemia	29.5	33.7	37.9
Nausea	26.3	28.4	34.5
Hot flush	21.1	21.1	20.7
Alopecia	18.9	20.0	27.6
Arthralgia	18.9	23.2	44.8
Diarrhoea	18.9	22.1	44.8
Decreased appetite	15.8	16.8	6.9
Headache	13.7	13.7	24.1
Vomiting	13.7	14.7	17.2
Dyspnoea	12.6	16.8	13.8
Nasopharyngitis	12.6	14.7	20.7
Thrombocytopenia	12.6	16.8	20.7
Asthenia	10.5	12.6	3.4

Cumulative Incidence of TEAEs (All Causality) in the First Year of Treatment, the First 2 Years of Treatment, and in those Subjects Treated for More Than 2 Years of With Palbociclib on Study A5481003 (Descending Order of Frequency for Events Reported at Incidences >10% in the First Year)

Adverse Events	First Year N = 95	First 2 Years N = 95	> 2 Years N = 29
Cough	10.5	13.7	20.7

2.6.3 Palbociclib and Tamoxifen

The potential for a drug-drug interaction between palbociclib and tamoxifen is considered to be probable. Multiple enzymes are responsible for the metabolism of tamoxifen and its active metabolites including CYP3A4, CYP2C9, and CYP2D6. In vitro evidence suggest that tamoxifen and one of its primary active metabolites, 4-hydroxy-tamoxifen, are inducers of CYP3A4 enzymes. In clinical trials, co-administration of tamoxifen with letrozole and anastrozole (both CYP3A4 substrates) has resulted in decreased exposures (AUC) of each by 37% and 27%, respectively. Palbociclib is a CYP3A4 substrate and CYP3A4 is thought to be the primary route of the oxidative metabolism of palbociclib. Thus, the co-administration of tamoxifen and palbociclib may lead to lower circulating levels of palbociclib and require an upward dose adjustment in palbociclib if these two compounds are used in conjunction. Additionally, time-dependent inhibition of CYP3A4 has been observed in preclinical studies of palbociclib, which could potentially impact the circulating steady-state levels of tamoxifen and its active metabolites.

A fixed-sequence 2-period crossover drug-drug interaction study to assess the effect of steady-state levels of tamoxifen and its active metabolites on the pharmacokinetics of single dose palbociclib in healthy volunteers has been conducted to rule out a need for palbociclib dose-adjustments when used in conjunction with tamoxifen (A5481026). The preliminary data collected from 25 subjects indicates a lack of clinically significant effect of tamoxifen on palbociclib exposure.

In order to assess the in vivo potential for palbociclib to act as a time-dependent inhibitor of CYP3A4, the pharmacokinetics of a single oral dose of midazolam, a sensitive CYP3A4 substrate, with and without palbociclib dosed to steady-state was assessed in a healthy volunteer drug-drug interaction study (A5481012). The results showed that geometric mean plasma midazolam C_{max} and AUC_{inf} values increased 1.37- and 1.61-fold, respectively, when a single oral dose of midazolam was co-administered with 125 mg dose of palbociclib

following 6 daily 125 mg oral doses of palbociclib as compared to its administration alone. This indicates that palbociclib is a weak time-dependent inhibitor of CYP3A4/5 following daily 125 mg dosing of palbociclib at steady-state.

An *in vivo* parallel cohort drug-drug interaction assessment has been included in the Phase 3 PENELOPE$_B$ Study to assess the potential for palbociclib to alter the circulating steady-state levels of tamoxifen and its active metabolites.

2.7 Quality of Life Analysis

Patient-reported outcomes (PRO) are an important part of new drug evaluation, and may play a role in regulatory approval of novel agents in oncology.[33] PROs are evaluated through the use of questionnaires developed to assess topics a patient can report about his or her own health. This includes symptoms (i.e. nausea, fatigue, diarrhea), physical functioning (difficulty climbing stairs or fastening buttons), and mental health (i.e. anxiety, fear or worry).

Previous studies have demonstrated that patient and clinician reports of symptoms during cancer treatment provide discrepant but complimentary information. [34-36] The current standard mechanism for reporting toxicities in cancer research is clinician-only reporting using items from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). In a retrospective analysis of 14 randomized clinical trials which utilized simultaneous patient and clinician reporting, PRO measures improved the predictive accuracy of clinician CTCAE reporting.[37] In a prospective study including lung cancer patients PRO measurements of toxicities better reflected patients' underlying state and functional status than clinician's evaluation.[35]

In the current study, we will assess patient-reported quality of life via the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) as well as fatigue via the Brief Fatigue Inventory (BFI) fatigue scale.

The EORTC QLQ C-30 instrument was designed to measure health-related quality of life of patients with cancer. It consists of 30 items grouped into the following subscales: general physical symptoms, physical functioning, fatigue/malaise, social functioning and psychological distress. The instrument has been validated in patients with cancer with a poor clinical status, who were demonstrated to report significantly lower levels of physical, social, role and emotional functioning and higher levels of fatigue, than those patients with a better clinical profile[38,39]. Further, the EORTC QLQ-C30 was sensitive to change over time from pre-chemotherapy to 8 days after chemotherapy in the expected directions for physical and social role functioning and global quality of life in breast, ovarian and lung cancer patients. [39]

2.8 Rationale

Preclinical data from both Pfizer and other laboratories suggest that luminal estrogen receptor positive cell lines are sensitive to CDK4/6

inhibition, which may reflect hyperactivation of cyclin D1-CDK4/6. Comprehensive blockade of ER+ signaling pathway is synergistic with cell cycle arrest and results in clinical benefit and extends PFS in hormonal receptor positive metastatic breast cancer.

Given the demonstrated benefits of palbociclib in metastatic HR+ HER2-negative breast cancer, there is interest in whether the benefits may translate into the adjuvant setting. Adjuvant endocrine therapy for breast cancer can be highly effective, however disease recurrence can occur, both in the first 5 years after a diagnosis and beyond 5 years. Trends in adjuvant endocrine therapy for HR+ breast cancer are moving towards longer duration therapy.[34] Large scale trials will be planned to determine whether the addition of palbociclib to adjuvant endocrine therapy will improve outcomes over endocrine therapy alone. An important and relevant question informing the design of these trials will be defining of the optimal duration of combination therapy, in terms of both feasibility and safety.

Innovations in treatment for metastatic breast cancer have often translated into substantial gains in disease-free or overall survival for earlier stage breast cancer. In phase I and II studies in metastatic breast cancer, palbociclib was generally well tolerated without significant adverse events, either as monotherapy or in combination with letrozole (see section 6.1.1 for specifics of toxicities observed). This documented tolerability supports that notion that risk/benefit assessment will favor the addition of palbociclib in the adjuvant setting as well, where the risks of adding a novel therapy are weighted more heavily in a patient population whose life expectancy may not be limited by malignancy. However, given the lack of safety data in the adjuvant curative setting, selection of a higher-risk subset of adjuvant breast cancer patients may appropriately balance potential risks and benefits of palbociclib therapy. Additionally, in clinical trials the commercially available AIs (letrozole, anastrozole, and exemestane) perform equivalently. In clinical practice, the toxicity profile of the three AIs is very similar and they are often used interchangeably, allowing design of a trial pairing palbociclib with any of the three commonly used AIs. Tamoxifen is a commonly used agent in both pre-and post-menopausal patients, can be used as extended duration therapy, and early studies have suggested no interactions with palbociclib.

Based on these existing questions, this trial has been planned to determine the feasibility of longer duration combination therapy with palbociclib and adjuvant endocrine therapy in patients with higher-risk HR+ breast cancer.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study. Testing required for eligibility must be completed within 14 days prior to study entry.

3.1.1 Patient/Disease Specifics:

- Participants must have histologically confirmed hormone receptor positive (HR+) HER2 negative stage II or stage III invasive breast cancer. Evaluation for metastatic disease is not required in the absence of symptoms.
- Men and pre- and postmenopausal women are eligible.

3.1.2 Prior Treatment Specifics:

- Participants may or may not have received (neo)adjuvant chemotherapy, but must be at least 30 days after last dose of chemotherapy and/or biologic therapy, with no more than grade 1 residual toxicity at the time of screening.
- Participants may or may not have received adjuvant radiotherapy, but must be at least 30 days after last dose radiotherapy, with no more than grade 1 residual toxicity at the time of screening.
- If most recent therapy was surgery, participants must be at least 30 days out from definitive surgery with no active wound healing complications.

3.1.3 Participants must have demonstrated ability to tolerate adjuvant endocrine therapy, either tamoxifen or aromatase inhibitor (AI), by prior successful completion of at least 1 month of endocrine therapy without significant adverse events, and in the opinion of the treating physician any ongoing toxicity does not preclude ability to continue on endocrine therapy for at least a projected 2 year continuous duration. Ongoing use of any AI, including letrozole, anastrozole, or exemestane, or tamoxifen is allowed. Concurrent GNRH agonist is allowable as well. Patients may enroll within 2 years of beginning endocrine therapy, as long as there is a plan for at least 2 more years of adjuvant endocrine therapy.

3.1.4 ECOG performance status 0-1 (see Appendix A).

3.1.5 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of palbociclib in combination with endocrine therapy in participants <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

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

- Absolute neutrophil count $\geq$ 1,500/μL
- Platelets $\geq$ 100,000/μL
- Hemoglobin $\geq$ 9g/dL
- Total bilirubin < 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 ≤ institutional upper limit of normal or creatinine clearance ≥ 60 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.
- Baseline QTc ≤ 480 ms

3.1.7 Premenopausal women must have a negative serum or urine pregnancy test. Pregnancy testing does not need to be pursued in female patients who are:

- Age ≥ 60 years; or
- Age < 60 with intact uterus and amenorrhea for 12 consecutive months or more AND estrogen (estradiol) levels within postmenopausal range; or
- Status-post bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation.

3.1.8 The effects of palbociclib 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 of childbearing age (who do not meet the criteria defined in 3.1.7), 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. 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.

H**ighly 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

3.1.9 Subject must be able to swallow and retain oral medication.

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

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Concurrent therapy with other investigational agents.

3.2.2 Prior therapy with any CDK4/6 inhibitor.

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

3.2.4 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 B, and can also be found within section 5.4. 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.

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

3.2.6 Subjects with organ allograft requiring immunosuppression.

3.2.7 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, uncontrolled diabetes mellitus, 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.

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

3.2.9 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.

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

Men and women are eligible for this protocol. Every effort will be made to include patients from minority populations.

4. REGISTRATION PROCEDURES

4.1 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 therapy. Any participant not registered to the protocol before treatment 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 must begin protocol treatment within 7 days. 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 may be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 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.

4.3 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 treatment during off-hours or holidays, call the QACT registration line at [redacted] 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 the 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 [redacted]
- 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.

4.4 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager. All sites should call the Project Manager [redacted] to verify treatment availability.

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

4.5 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and emailed to [redacted]

- Clinic visit note documenting history and physical exam
- Copy of required laboratory tests including: Hematology (CBC with differential), serum chemistries (creatinine and/or creatinine clearance, bilirubin, ALT, and AST)
- Pathology report and documentation of ER/PR status and HER2 status.
- ECG report
- Signed participant consent form
- HIPAA authorization form (if separate from the informed consent document)
- Completed QACT Eligibility checklist

To complete the registration process, the Project Manager will

- register the participant on the protocol with the QACT
- e-mail the confirmation of registration with the participant study number, to the participating site
- call the research nurse or data manager at the participating site and verbally confirm registration

NOTE: Registration and randomization with the QACT can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and

discussion with the DF/HCC Project Manager.

5. TREATMENT PLAN

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.

5.1 Overall Study Design and Plan

This is a non-randomized, open label study of the feasibility of longer duration combination therapy with palbociclib and adjuvant endocrine therapy in patients with higher-risk HR+ breast cancer. Each subject will be assigned a unique identification number during screening, which will be used on all case report forms (CRFs) and correspondence regarding the subject.

Treatment Description					
Agent	**Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Palbociclib	Given with food	125 mg	PO	Daily on days 1-21, followed by one week off	28 days (4 weeks)
One of the following agents: (1) Letrozole (2) Anastrozole (3) Exemestane (4) Tamoxifen	None for letrozole, anastrozole, tamoxifen; for exemestane: suggested to take after a meal	- Letrozole 2.5 mg, or - Anastrozole 1 mg, or - Exemestane 25 mg - Tamoxifen 20 mg	PO	Daily, continuous	

Endocrine therapy is not prescribed by the trial but should consist of the agent on which the patient has demonstrated tolerability and stability for at least the previous 1 month. Treatment with combination therapy will be planned for a goal duration of 2 years. The start of a cycle is defined as the day when palbociclib administration begins.

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 do not need to be repeated.

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 3.1.6, are CBC with differential, chemistries, and EKG. Pregnancy testing for screening should be obtained in appropriate patients, as defined in Eligibility. 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 < 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 $\leq$ institutional upper limit of normal or creatinine clearance $\geq$ 60 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.
- Baseline QTc $\leq$ 480 ms
- Negative pregnancy test in appropriate patients
- HgA1C (no required threshold level for initiation of therapy)

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.

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

5.3.2 Endocrine Therapy AI: letrozole, anastrozole, exemestane

Endocrine therapy (letrozole, anastrozole, exemestane, or tamoxifen) should be taken orally, once per day, as per standard dosing. Ordering of endocrine therapy self-administration relative to palbociclib self-administration is as per patient preference. A drug diary is supplied in Appendix D, for patients' use to record dosing. In addition, patients will bring pill bottles and drug diaries to visits. .

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

Growth factors, including GCSF, are not allowed on trial. Concurrent metformin is allowable.

Cautious administration of a medication listed in Appendix F is permitted if absolutely medically necessary and with close QT monitoring. These cases must be discussed with the overall PI prior to administration of a medication from this list.

The use of concurrent investigational or other antitumor therapies, other than endocrine therapy, is not permitted. It is permitted to switch among members of the AI class (letrozole, anastrozole, and exemestane), or from AI to tamoxifen or vice versa, while on trial.

Missed doses of either endocrine therapy or palbociclib are not made up.

If a patient finds she is not able to continue to tolerate endocrine therapy and is considering stopping endocrine medication altogether, she must stop all protocol therapy and will be removed from trial for lack of tolerability of combination therapy. For a patient who comes off protocol therapy, it is strongly encouraged to resume endocrine therapy once symptoms resolve, or change to alternative endocrine therapy.

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 B.

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

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.

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

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

Surgery is allowed during protocol therapy, however it is suggested to avoid nadir of counts at time of surgery. Patients pursuing surgery must hold palbociclib therapy 7 days before the surgery and up to 3 weeks after surgery. Patients pursuing DIEP reconstruction may have palbociclib held for up to 5 weeks after surgery. Patients may resume palbociclib therapy once satisfactory wound healing and recovery have occurred. Patients should continue endocrine therapy if palbociclib is held for surgery.

5.5 Duration of Therapy

Total duration of combination therapy with palbociclib and endocrine therapy will be 2 calendar years. The last cycle of therapy should not be interrupted at 2 years. If a new cycle of therapy was started $\geq$ 1 week prior to the completion of two years of therapy, that cycle should be completed. If the last cycle of therapy is completed < 1 week prior to the completion of two years, a new cycle should not be

initiated. Missed doses are not made up. Any one of the following criteria will be reason to stop therapy before 2 years:

- Development of recurrent disease by clinical evaluation, with need to change systemic therapy,
- Intercurrent illness that prevents further administration of combination treatment,
- Unacceptable toxicity of either palbociclib or endocrine therapy,
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements, including adherence to oral therapy, as determined by the treating provider,
- Patient is unable to take either oral medication for more than 4 weeks, for any reason,
- Provider preference for patient to come off study,
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

If a patient finds she is not able to continue on combination therapy and must stop protocol therapy, she is strongly encouraged to resume endocrine therapy once symptoms resolve, or change to alternative endocrine therapy.

5.6 Duration of Follow Up

Participants will be followed for 30 days after removal from study or until death, whichever occurs first. Participants removed from study for serious adverse events (SAEs) will be followed until resolution or, if resolution is unlikely, until the event or sequelae stabilize.

5.7 Criteria for Removal from Study

The investigator may withdraw a subject from the study at any time for safety or administrative reasons. A subject may stop study treatment at any time for safety or personal reasons.

Subjects who withdraw after signing the informed consent form (ICF) but before receiving study treatment will be replaced.

Participants will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with and, if necessary, provided for the participant.

A subject who has ceased to return for visits will be followed up by mail, phone, or other means as much as possible to gather information

such as the reason for failure to return and the status of treatment compliance, presence or absence of AEs, the clinical course of signs and symptoms, and survival.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Erica L. Mayer MD MPH at [redacted]

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. See Appendix C for an overview of CTCAE.

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 6.3. In the event treatment interruption is deemed necessary for either palbociclib or the endocrine therapy, treatment with the other medication will continue as planned.

As per section 5.4, treatment with growth factors is not allowed on trial.

If the retreatment parameters (see section 6.3) are met within 4 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 4 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should permanently discontinue palbociclib treatment.

Patients holding palbociclib for surgery are allowed to hold 7 days before and up to 4 weeks after surgery, and are allowed to resume palbociclib therapy once satisfactory wound healing and recovery have occurred. . Patients pursuing DIEP reconstruction may have palbociclib held for up to 5 weeks after surgery. Patients should continue endocrine therapy if palbociclib is held for surgery.

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

6.1.2 Toxicity management – Endocrine Therapy

No dose reduction for endocrine therapy is permitted, but dosing interruptions are allowed (see section 6.2.). Treatment interruptions for up to 3 cumulative weeks for endocrine therapy -related toxicities or personal reasons are allowed as per the investigator's best medical judgment. Rotation of AI therapy among the three approved agents is also allowed, as is change to AI from tamoxifen or change to tamoxifen from AI.

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

6.2 Palbociclib 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.

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

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

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

If a new cycle of therapy was started >_1 week prior to the completion of two years of therapy, that cycle should be completed even it requires treatment to extend past 2 years.

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 4 weeks;
- Grade 3 QTc prolongation (QTc ≥501 msec on at least two separate ECGs);
- Grade 3 or 4 increased ALT or AST;
- In case of concurrent > 3x ULN ALT and 2x ULN Total Bilirubin, palbociclib will be permanently discontinued.

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

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

6.2.2 Palbociclib Retreatment Criteria

Retreatment with palbociclib following treatment interruption for treatment related toxicity or at the start of a new cycle that requires a clinic visit (Cycles 2, 3, 4, 6, 8, 10, 12, 15, 18, 21, 24) may not occur until all of the following parameters have been met:

- Platelet count ≥ 75,000/mm^3;
- ANC ≥ 1000/mm^3 and no fever;

- Any 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.

The start of new cycles that require labs without a clinic visit may begin without receiving results for required labs (CBCs). The nurse or physician should contact the patient when the lab results are available to instruct them to modify treatment if abnormal labs requiring a treatment hold are noted. Lab results must be available by Day 3 of each cycle.

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

If the retreatment parameters are met within 4 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Please refer to Dose Reductions Section for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 4 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should permanently discontinue palbociclib treatment.

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 (<4 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 ≥4 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/d
-1	100 mg/d
-2	75 mg/d
	Discontinue Study Treatment

Palbociclib recommended dose modifications for treatment-related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 2.

Table 2. Palbociclib Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment.

Toxicity	Intervention with Palbociclib
Uncomplicated Grade 3 neutropenia *(ANC ≥500 - <1000/mm^3)*	• 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 4 weeks, then resume drug and decrease drug by 1 dose level. • Recurrent uncomplicated Grade 3: Hold drug. If ANC recovers (ANC ≥ 1000) within 2 weeks, resume drug and decrease drug by 1 dose level.
Grade 3 neutropenia *(ANC<1000/mm^3)* **associated with a documented infection or fever ≥38.5°**	• 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 4 weeks, then resume drug and decrease drug by 2 dose levels. • If these parameters have not been met after 4 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 ≥ 75,000, then resume drug and decrease by 1 dose level. • Recurrent Grade 3 thrombocytopenia: hold drug until plt ≥75,000, 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 4 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.

Grade 3 or 4 increased ALT or AST	• 1st occurrence: Hold drug until clinically stable and decreases to ≤ Grade 1, then resume drug and decrease by 1 dose level • 2nd occurrence: Discontinue drug
LFTs Concurrent > 3XULN SGPT/ALT and 2X ULN total bilirubin (Hy's Law)	Discontinue Palbociclib 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 F]).

All cases of QTc prolongation should be discussed with the overall PI prior to dose modification or discontinuation of therapy. Recommended dose modifications in the event of QTc prolongation are provided in the Table below.

Palbociclib Dose Modifications in the Event of QTc Prolongation

	Toxicity (NCI CTC Grade, Version 4.0)		
	Grade 2 QTc prolongation (>480 and <500 msec, or 60 msec above baseline)	**Grade 3 QTc prolongation** (≥ 501 msec)	**Grade 4 QTc prolongation** (≥ 501 msec or >60 ms change from baseline and 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 intoconsideration 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 Dose modifications/delays – Endocrine Therapy

No dose reduction for endocrine therapy is permitted, but dosing interruptions are allowed. Treatment interruptions for up to 3 cumulative weeks for endocrine therapy-related toxicities or personal reasons will be performed as per the investigator's best medical judgment. Palbociclib should not be held during endocrine therapy interruption, unless palbociclib is on hold for a separate reason as described in section 6.2.1. Rotation of AI therapy among the three approved agents is also allowed, as is change to AI from tamoxifen or change to tamoxifen from AI.

If a patient requires 2 endocrine therapy holds up to 4 weeks within a 6 month period of time, the treating physician should consider whether a patient needs to be removed from study for treatment-related toxicity. If a patient needs more than 2 endocrine therapy holds up to 4 weeks within a 6 month period of time, the patient will have to be removed from study for intolerance of combination therapy. Once recovered, the patient should be encouraged to continue adjuvant endocrine therapy.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Expected Toxicities

7.1.1 Adverse Event List(s) for Palbociclib

The primary anticipated toxicity of palbociclib is neutropenia. In the phase I, dose-escalation trial of palbociclib alone in advanced cancers[35], 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%).[31] 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.[32,33] 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,[35] QT interval changes were also evaluated in detail. While 26 of 41 patients had a maximum increase of <30 msec from baseline QTc, zero patients had an on-treatment value exceeding 500 msec.

7.1.2 Adverse Event List(s) for Commercial Agent(s) – AIs (letrozole, anastrozole, exemestane) and Tamoxifen

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

Package inserts for the 3 AIs and tamoxifen can be found at:

- Letrozole: http://www.pharma.us.novartis.com/cs/www.pharma.us.novartis.com/product/pi/pdf/Femara.pdf
- Anastrozole: http://editor.apppharma.com/PIs/Anastrozole_451221_Apr_10.pdf
- Exemestane: http://patient.cancerconsultants.com/druginserts/Exemestane.pdf
- Tamoxifen: http://patient.cancerconsultants.com/druginserts/Tamoxifen.pdf

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

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. Serious AEs will be followed until resolution or, if resolution is unlikely, until the event or sequelae stabilize.

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

7.3.1 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.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Table 3: DF/HCC Reportable AEs

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

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

7.4 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.

7.5 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.

7.5.1 SAE Definition.

An SAE is any adverse event, without regard to causality, that is life-threatening (ie, 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 (ie, substantial disruption of the ability to conduct normal life functions); or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

7.5.2 Exposure During Pregnancy, Exposure During Lactation, Occupational Exposure

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

7.5.3 Hy's Law Cases

Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable to 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.

7.5.4 Exclusions from SAE Reporting Requirements

Specifically excluded from the reporting requirements for SAEs under this provision is any SAE identified in the Protocol as anticipated to occur in the Study population at some frequency independent of drug exposure, unless the Principal Investigator assesses such an event as related to the Palbociclib. Also specifically excluded from the reporting requirements is any SAE judged by the Overall Investigator to represent progression of the malignancy under study, unless it results in death within the SAE Reporting Period.

7.5.5 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.

7.6 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

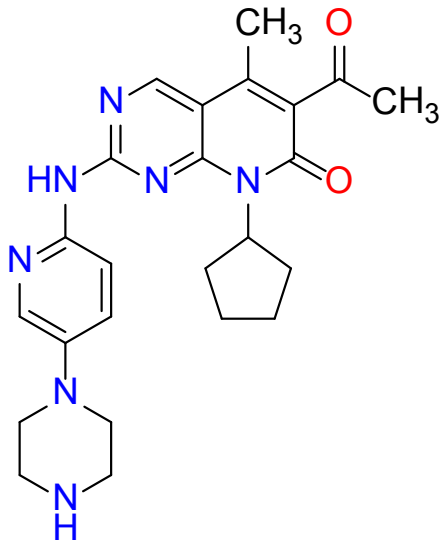
All adverse events, regardless of relationship to study treatment or grade, will be collected from the time the subject initiated therapy until 30 days after discontinuation of study treatment. All AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first. 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 or other agents administered in this study can be found in Section 7.1.

8.1 Palbociclib

8.1.1 <u>Description</u>



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: ~27 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 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
75 mg	Sunset Yellow/Sunset Yellow	2
100 mg	Caramel/Sunset Yellow	1
125 mg	Caramel/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 any of the three AIs.

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 is an investigational agent 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 can be obtained by contacting the DFCI project managers at: [redacted]

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, 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.)

8.1.10 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 Letrozole

8.2.1 Description

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

8.2.2 Form

Letrozole is available in 2.5 mg tablets.

8.2.3 Storage and Stability

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

8.2.4 Compatibility

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

8.2.5 Availability

Letrozole is commercially available.

8.2.6 Administration

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

8.3 Anastrozole

8.3.1 Description

Anastrozole tablets for oral administration contain 1 mg of anastrozole, a non-steroidal aromatase inhibitor. It is chemically described as 1,3-Benzenediacetonitrile, a, a, a', a'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). Anastrozole is an off-white powder with a molecular weight of 293.4. Ansastrozole has moderate aqueous solubility (0.5 mg/mL at 25˚C); solubility is independent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol, and tetrahydrofuran, and very soluble in acetonitrile.

8.3.2 Form

Anastrozole is available in 1 mg tablets.

8.3.3 Storage and Stability

Store at 20˚ to 25˚C (68˚- 77˚F) [see USP Controlled Room Temperature].

8.3.4 Compatibility

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

8.3.5 Availability

Anastrozole is commercially available.

8.3.6 Administration

The recommended dose of anastrozole is one 1mg tablet taken once daily.

8.4 Exemestane

8.4.1 Description

Exemestane tablets for oral administration contain 25 mg of exemestane, an irreversible, steroidal aromatase inactivator. Exemestane is chemically described as 6-methylenandrosta-1,4-diene-3,17-dione. The active ingredient is a white to slightly yellow crystalline powder with a molecular weight of 296.41. Exemestane is freely soluble in N, N-dimethylformamide, soluble in methanol, and practically insoluble in water.

8.4.2 Form
Exemestane is available in 25 mg tablets.

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

8.4.4 Compatibility
No compatibility issues exist for co-administration of palbociclib and exemestane.

8.4.5 Availability
Exemestane is commercially available.

8.4.6 Administration
The recommended dose of exemestane is 25 mg once daily after a meal.

8.5 Tamoxifen

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

8.5.2 Form
Tamoxifen is available in 20 mg tablets.

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

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

8.5.5 Availability
Tamoxifen is commercially available.

8.5.6 Administration
The recommended dose of tamoxifen is 20 mg once daily.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Research Specimen Collection

A whole blood sample will be collected pretreatment on Cycle 1 Day 1 to be retained for potential pharmacogenomic analyses related to drug response or adverse drug reactions. If sample is not collected on C1D1 it can be collected any time prior to the end of protocol treatment.

Methods: 1 10ml EDTA tube will be collected pretreatment on the Cycle 1 Day 1 visit for all participating patients. Specimens should be labeled with the assigned sample ID number, date of collection, time point of collection, and protocol number.

- Complete the 13-559 Specimen Requisition form found in Appendix E.
- Ship the same day as collection at ambient temperature by overnight courier to:

Dana Farber Cancer Institute
[redacted]

All research blood samples should arrive during the week by Friday morning.

Email [redacted] and DFCI Study Coordinator with the sample information and tracking information the day before shipping specimens.
[redacted]

If the blood must be drawn on a Friday or the day before a holiday, sites can aliquot the whole blood into 4 cryovials and freeze them at -80C, then ship on dry ice Monday-Thursday.

The coordinating center study coordinator will track the research blood specimens using CaTissue. Upon receipt of an email notification regarding sample shipment from a participating site, the coordinating center study coordinator will log in the sample information into CaTissue. When the sample is received by the staff at the DF/HCC Core Blood and Tissue Bank lab, the confirmation of receipt and specimen location information will be added to CaTissue. CaTissue will contain a complete record of the research blood samples that are collected as part of this study.
All samples will be de-identified and assigned a linked sample ID number on arrival; all participant identification will be removed.

In patients who develop recurrent disease during protocol therapy, tumor biopsy and collection of a sample of whole blood are strongly recommended. Samples may be analyzed by whole exome sequencing on archival vs. recurrent tumor to evaluate pathways of palbociclib and endocrine resistance. Biopsy and collection of blood at progression are not part of this clinical trial.

9.2 Quality of Life

The QOL survey (EORTC QLQ-C30) will be administered at Baseline/Cycle 1 day 1, Cycle 3 day 1, Cycle 6 Day 1, Cycle 12 Day 1, Cycle 18 Day 1, and End-of-Treatment visit. The survey will be administered as paper copies at all sites, and all sites should retain copies of the completed surveys for source documentation. Patients can complete the survey either before or after the provider visit. Copies of all survey items are available in Appendix I.

9.3 Drug Adherence

Drug diaries (Appendix D) will be maintained for patients to capture adherence to oral palbociclib and endocrine 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 with endocrine therapy, their provider may remove them from the trial (as described in Section 5.5).

10. STUDY CALENDAR

10.1 Schedule of Visits

Table 4 summarizes the Study Calendar. Visits should occur within +/- 3 days of the scheduled day unless otherwise specified. If a subject fails to appear for a scheduled study visit, the investigator will make every attempt to contact the subject and determine the reason(s) for the missed visit as completely and accurately as possible. Subjects will only be judged as lost to follow-up if they cannot be reached after three documented attempts (1 week apart) by the site to contact them.

Treatment visits

Patient will be seen monthly for the first 4 cycles of therapy, then every 2 cycles through Cycle 12 and then every 3 cycles for year 2. More frequent visits are acceptable if necessary for closer monitoring of toxicity.

Additional monitoring for neutropenia will consist of CBC with differential performed:

- Day 1 and 15 of Cycles 1-3: Day 1 CBCs for Cycles 1-3 must be drawn within 3 days prior to starting a new cycle. Day 15 CBCs for Cycles 1-3 must be drawn +/- 3 days.
- Every 2 cycles (+/- 7 days) for Cycles 4-12
- Every 3 cycles (+/- 7 days) during Year 2 (i.e., C15D1, C18D1, C21D1, C24D1, and End of treatment)

CBCs may be drawn either at the treatment center or at a home clinic when not being seen at the treatment center, for the duration of therapy. This laboratory testing can be done locally with results faxed to the treatment team; however, treatment should not begin or resume until the results have been reviewed.

ECGs will be performed at screening visit, then Day 1 of Cycles 1-4, then every 2 cycles through Cycle 12 and then every 3 cycles for year 2. ECGs will be performed using institutional machines and may be performed up to 72 hours prior to the start of a new cycle.

End-of-treatment visit

Subjects will continue to receive study treatment for 2 years or until meeting another withdrawal criterion.

All subjects will be asked to return to the site for a final, End-of-Treatment visit, if possible. The End-of-Treatment visit must be performed within 30 days of final administration of study treatment. End-of-treatment assessments will not have to be repeated if the same assessments were performed within 7 days of this visit.

Chemistry and Hematology assessments are required 30 days after the completion of protocol therapy or early discontinuation of treatment. Labs can be done locally.

For patients on treatment who have documented grade 2 or higher fatigue or newly documented grade 2 or higher fatigue, it is suggested to have testing performed to assess vitamin B12 levels.

Table 5. Study Calendar

	Pre-Study	**Treatment phase (2 years total)** Treatment visits will occur every 4 weeks for the first 4 cycles of palbociclib therapy, then every 8 weeks through Cycle 12, then every 12 weeks for year 2. 4 weeks (28 days) = 1 cycle											**Off Study**[o]
Cycle (C)		**C1-3**	**C1-3**	**C4**	**C6**	**C8**	**C10**	**C12**	**C15**	**C18**	**C21**	**C24**	
Day (D)[a]	**-14 to 0**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Informed consent *(perform within 28 days of registration)*	X -28 to 0												
Inclusion/Exclusion criteria	X												
Demographic data	X												
Medical/surgical history	X												
Prior medications/ procedures	X												
Pregnancy test[b]	X												
ECOG PS[c]	X	X		X	X	X	X	X	X	X	X	X	X
12-lead EKG[d]	X	X		X	X	X	X	X	X	X	X	X	
Physical examination	X[m]	X		X	X	X	X	X	X	X	X	X	X
Vital signs[e]		X		X	X	X	X	X	X	X	X	X	X
Hematology[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hemoglobin A_{1c} (HbA_{1c})[g]	X	C3 only			X	X		X	X	X	X		X
Chemistry[h]	X	X		X	X	X	X	X	X	X	X	X	X
Vitamin B12[i]	X			X									
Whole Blood Sample[j]		C1 only											
Perform pill count		X		X	X	X	X	X	X	X	X	X	X
AE evaluation[k]	X	X		X	X	X	X	X	X	X	X	X	X
Concomitant meds[l]	X	X		X	X	X	X	X	X	X	X	X	X

QOL Surveys (See section 9.2)	X	X[n]			X			X		X			X

a: Assessments on Day 1 of each cycle may be performed within 3 days prior to the start of a new cycle.
b: Premenopausal patients must have a negative serum or urine pregnancy test. See section 3.1.7.
c: See Appendix A for ECOG PS definitions
d: ECGs will be performed at screening visit, then Day 1 of Cycles 1-4, then every 2 cycles through Cycle 12 and then every 3 cycles for year 2. ECGs will be performed using institutional machines and may be performed up to 72 hours prior to the start of a new cycle. ECGs are not required on Day 1 of Cycle 1 if performed within 72 hours before study administration.
e: Vital signs should include: BP, HR, respiratory rate, body temperature and weight
f: Hematology assessment consists of CBC with differential. Hematology assessments are not required on Day 1 of Cycle 1 if performed within 3 days before study administration. Day 1and 15 CBCs for all cycles must be drawn +/- 3 days. CBCs drawn on non-MD visit days can be drawn at a local lab results submitted to study team. See Section 6.2.2 for re-treatment instructions.
g: Hemoglobin A_{1c} is performed at pre-study, Day 1 of Cycle 3, 6, 8, 12, 15, 18, 21, and at Off-Study visit.
h: Chemistry assessment consists of a complete metabolic panel ("chem 12"). Chemistry assessments are not required on Day 1 of Cycle 1 if performed within 3 days before study administration. Day 1 chemistries for subsequent cycles must be drawn +/- 3 days. See section 6.2.2 for re-treatment instructions.
i: B12 assessments are to be performed at baseline, C4D1, and again in any setting of grade 2 fatigue. Patients who have already started treatment should have B12 assessments performed at C4D1, and again in any setting of grade 2 fatigue. Patients who have already documented grade 2 fatigue or newly documented grade 2 fatigue should have the B12 assessment performed at their next study visit.
j: See Section 9 for specimen collection requirements.
k: All AEs will be collected from the time the subject initiated therapy until 30 days after discontinuation of study treatment. See Section 7 for additional information.
l: Record all prior and concomitant medication use (prescription and nonprescription medications as well as transfusions) beginning 30 days before the start of study treatment (except record all previous breast cancer treatments)
m: Baseline Physical Exam may be performed up to 7 days prior to day 1 of Cycle 1
n: QOL survey to be completed before treatment begins (baseline or day 1 of Cycle 1) and day 1 of Cycle 3.
o: These assessments will also be conducted upon early discontinuation from the study. Off study evaluation should be completed within 30 (+/- 7) days of the last day of protocol treatment.

11. MEASUREMENT OF EFFECT

Tumor response is not the primary endpoint of this trial; therefore Response Evaluation Criteria in Solid Tumors (RECIST) will not be used to aid in measurement of effect.

The primary endpoint of the study will be time from initiation of palbociclib to discontinuation of treatment due to toxicity, withdrawal of consent to be treated, or other events related to tolerability. The decision to remove a patient from the study will be made by the treating provider. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Patients who recur, withdraw consent to be followed, or complete 2 years of therapy will be censored at that time point.

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 Multicenter Guidelines

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

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the site has been activated

12.4 Collaborative Agreements Language

Not applicable

13. STATISTICAL CONSIDERATIONS

This is a single arm phase 2 pilot study of the feasibility of adding the agent palbociclib to adjuvant endocrine therapy. Eligible patients have high-risk hormone receptor positive breast cancer. Patients must have tolerated 1 month of exposure to endocrine therapy, and may enroll up to 24 months after beginning endocrine therapy, and must have a plan to complete at least 2 more years of therapy.

13.1 Study Design/Endpoints

Primary objective:

- To evaluate the treatment discontinuation rate at 2 years for patients receiving combination therapy with endocrine therapy and palbociclib

Secondary objective:

- To evaluate treatment discontinuation rates in the subgroups of patients that receive AI and tamoxifen-based therapy
- To describe the safety of extended duration therapy with palbociclib and endocrine therapy

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

A sample size of 160 patients is planned. Prior exposure to adjuvant chemotherapy will be collected prospectively, and capped at 120 patients such that at least 25% of enrolled patients will not have had exposure to adjuvant chemotherapy.

Patients who develop progressive disease before completing the first 6 months of protocol therapy will be replaced. It is expected no more than 5% of the study population would progress on study and need replacement. Subjects who withdraw after signing the informed consent form (ICF) but before receiving study treatment will be replaced.

The primary endpoint of the study will be time from initiation of palbociclib to discontinuation of treatment due to toxicity, withdrawal of consent to be treated, or other events related to tolerability. Patients who recur, withdraw consent to be followed, or complete 2 years of therapy will be censored at that time point.

If the true rate of discontinuation by two years is 48% or higher, the treatment duration will be considered not feasible and not worthy of further study. If the treatment rate of discontinuation is 33.3% or less, the treatment duration will be deemed feasible and worthy of further study.

The primary analysis of treatment discontinuation will be based on a landmark time analysis at two years, reported with a two-sided 95% confidence interval, and thresholds to an exact Binomial test chosen to strictly control the Type I error rate for the evaluable patient population, For example, with 128 uncensored patients, the null hypothesis is rejected if 50 or fewer failures are observed. Secondary analyses will report the rate of discontinuation at 1 year, and the full survival function will be estimated using the Kaplan-Meier method and a 95% confidence band with Greenwood formula for the standard deviation.

The first interim analyses for futility is scheduled to occur at the time that 50% of the target patients have received treatment, n=80. The second interim analysis is scheduled to occur at the time that 100% of the target patients have ended protocol treatment or received at least 6 months of therapy. As a conservative approach to assessing futility for the primary endpoint of discontinuation by two years, the observed proportion of discontinuations among all treated patients will be applied to a Beta-Binomial model, and a decision rule based on there being less than a 5% predicted probability of rejecting the null at the final analysis. If a determination of futility is made, the study will cease and treatment duration of two years will be considered not feasible. Further, p-values from the primary analysis will not be downwardly corrected to adjust for the interim futility analyses. Results of the interim analysis will be made available for presentation after final analysis is complete.

Within the subgroups of patients that receive an AI or tamoxifen for endocrine therapy, the Kaplan-Meier method and a 95% confidence band will be used to estimate survival functions.

13.2 Sample Size/Accrual Rate

Using a one-sided alpha = 0.025, there will be greater than 90% power to reject the null hypothesis in favor of feasibility with 128 subjects. A total sample size of 160 patients is planned to account for a censoring rate of 20% for the primary endpoint.

Accrual is anticipated to be approximately 10 patients per month, such that there would be 18 months of patient accession, and 24 months of follow-up until the final analysis.

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	16		+	0		=	16	
Not Hispanic or Latino	144		+	0		=	144	
Ethnic Category: Total of all subjects	160	(A1)	+	0	(B1)	=	160	(C1)
Racial Category								
American Indian or Alaskan Native	2		+	0		=	2	
Asian	16		+	0		=	16	
Black or African American	16		+	0		=	16	
Native Hawaiian or other Pacific Islander	2		+	0		=	2	
White	124		+	0		=	124	
Racial Category: Total of all subjects	160	(A2)	+	0	(B2)	=	160	(C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)	

13.3 Analysis of Secondary Endpoint: Safety of Extended Duration Therapy with Palbociclib and Endocrine Therapy

All patients who receive at least one dose of the study regimens will be included in the assessment of adverse events (full analysis population). Adverse event information for the two cohorts will be combined. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, and ECGs. Abnormal laboratory values will be flagged.

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; Appendix C.) Investigators will collect all CTCAE grades for all AEs (to assess both increasing and decreasing severity). Events will be summarized by frequency and percentage.

The incidence of TEAEs and relatedness to study treatment will be summarized. Although an adverse event may be reported more than once for a subject, that subject will be counted only one time in the incidence count for that adverse event term by the highest CTCAE grade (in the summary by CTCAE grade) and by the closest causal relationship to study treatment (in the summary by relatedness to study treatment).

Continual assessment of toxicity is planned, including specifically a monthly assessment of the total number of cases of Grade 3 or 4 (ANC<1000/mm^3) febrile neutropenia. Events are

categorized according to CTCAE 4.0, and if 5 or more cases are observed, irrespective of attribution, an assessment will be made by the study team as to the dose and schedule of medication. Accrual and treatment will not be suspended during the assessment. When performed sequentially for all 120 enrolled patients, this decision rule would have a 90% chance of triggering a review if the true risk of febrile neutropenia is 6.5% and less than a 10% chance of triggering a review if the true risk is 2.0%. Further, a 10% rate of all neutropenia AEs will be used as a non-binding threshold with the monthly review to inform decisions on dose and schedule.

13.4 Reporting and Exclusions

13.4.1 Evaluation of Toxicity

All participants who have received at least one dose of study medication will be evaluable for toxicity from the time of their first treatment.

13.4.2 Evaluation of Response

All participants who have received at least one dose of study medication will be assessed for the primary endpoint (time from initiation of palbociclib to discontinuation of treatment due to toxicity, withdrawal of consent to be treated, or other events related to tolerability).

13.5 Analysis of Quality of Life Assessments

The QOL data presentation and analysis will be descriptive and exploratory in nature. Descriptive statistics will be presented for the quantitative scores at baseline and each follow-up timepoint using the validated scales for the EORTC QOL instrument. Absolute change from baseline to each timepoint during treatment will be summarized and evaluated using a Wilcoxon signed rank test.

We anticipate that 80 patients will be enrolled after the amendment to include the QOL objective, and that 85% will provide complete information for paired tests. Under Gaussian assumption, there will be 90% power to detect a change from baseline of 0.36 standardized units using a two-sided alpha = 0.05. Scores will also be summarized graphically over the repeated assessments, and linear mixed effects models will be used to explore a QoL response profile over the course of treatment. The impact of missing data will be assessed using graphical methods to explore the patterns of missing assessments, and baseline patient/disease characteristics will be compared between patients who do and do not provide complete QOL data. Primary analyses will be performed using all available data.

14. PUBLICATION PLAN

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation. The Primary Investigator will be the final arbiter of the manuscript content.

The outcome results of this trial will be made public within 24 months of the end of data collection. Interim results of this trial may also be periodically presented at meetings of the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium. Results of the formal interim analysis will be made available for presentation after analysis is complete. A full report of the outcomes will be made public no later than two (2) years after the end of data collection.

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APPENDIX A: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS CRITERIA

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

APPENDIX B: 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:
Bosntan
Efavirenz
Etravine
Modafinil

Nafcillin

APPENDIX C: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (VERSION 4.0)

Cancer Therapy Evaluation Program, NCI CTCAE v 4.0. Available from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev 4.pdf.

APPENDIX D: 13-559 STUDY PARTICIPANT SELF-ADMINISTERED DRUG DIARY

PATIENT INSTRUCTIONS:

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

- Keep Palbociclib capsules in the bottle(s) provided and do not transfer them to any other container. Store at room temperature.
- Palbociclib should be taken by mouth once per day. Palbociclib should be taken with food.
    - During Cycles 1, 2 and 3 you will have blood work done on Day 15. Please do not take the next day's drug (Day 16) until a provider calls you to discuss the results.
- Capsules must be swallowed whole. Do not soak capsules or empty contents into any food or drink.
- If you vomit after taking Palbociclib, do NOT take another dose. Please note any vomiting in the **Comments** section of the diary on the next page.
- If a dose is missed and it is less than 6 hours from usual time of dosing, then you may take that dose. Otherwise that dose should be skipped and NOT taken. You should resume regular dosing the following day. If you miss a dose, record "0" for Number Taken on the next page.
- If you accidentally take an extra dose during a day skip the next day's dose and record the extra dose on the next page.

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

13-559 STUDY PARTICIPANT SELF-ADMINISTERED DIARY

Participant Name: _____ Cycle #: _____

Your Doctor _____ Phone _____

Your Nurse _____ Phone _____

PALBOCICLIB (Cycles 1-3)

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

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

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

Patient Signature: _____ Date: _____/_____/_____

13-559 STUDY PARTICIPANT SELF-ADMINISTERED DIARY

Participant Name: _____ Cycle #: _____

Your Doctor _____ Phone _____

Your Nurse _____ Phone _____

PALBOCICLIB (Cycle 4 and all remaining cycles)

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: _____/_____/_____

Participant Name: _____ Cycle #: _____

ENDOCRINE THERAPY

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

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

Patient Signature: _____ Date: _____/_____/_____

13-559 STUDY PARTICIPANT SELF-ADMINISTERED DRUG DIARY

Participant Name: _____ Cycle #: _____

OTHER MEDICATIONS TAKEN: Please list any daily medications (prescribed or otherwise) that you take. Use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

Drug Name	Dose	Dates Taken	Reason Taken

SYMPTOMS/SIDE EFFECTS: Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended.

Symptom	Start Date	End Date

APPENDIX E: 13-559 SPECIMEN REQUISITION FORM

Complete this form and include with the specimen shipment. Label ALL materials with participant initials, DFCI participant study ID, and the date the specimen was obtained.

Ship specimen(s) at ambient temperature to:

Dana-Farber Cancer Institute
[redacted]

Specimen Information
Participant Initials (FML): _____ DFCI Participant Study ID Number: _____

Time period: ☐ Pre-treatment Cycle 1 Day 1 Date specimen(s) shipped: _____

Specimen Type *(indicate inclusion in shipment by checking box)*	**Quantity submitted**	**Date specimen collected**
☐ 10 mL Whole Blood in lavender top (EDTA) tube		
☐ Other, specify:		

Responsible contact: _____

Email: _____

Phone number: _____

Site: _____

APPENDIX F: LIST OF DRUGS KNOWN TO PREDISPOSE TO TORSADE DE POINTES

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
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 G: DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLAN

DFCI IRB Protocol #: **13-559**

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1.0 INTRODUCTION

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

1.1 Purpose

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

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

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

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

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

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

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is

the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Quality Assurance Office for Clinical Trials: A unit within DF/HCC developed to computerize and manage data, and to provide a Quality Control and Quality Assurance function for DF/HCC trials.

2.0 GENERAL ROLES AND RESPONSIBILITIES

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

2.1 DF/HCC Sponsor

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

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

2.2 Coordinating Center

The Coordinating Center will assume the following general responsibilities:

- Assist in protocol development
- Maintain copies of Federal Wide Assurance and Institutional Review Board (IRB) approvals from all Participating Institutions.

- Maintain FDA correspondence, as applicable.
- Maintain updated roster of participants.
- Verify eligibility.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to DF/HCC Sponsor for timely review.
- Distribute adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all participating investigators.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Monitor Participating Institutions either by on-site or virtual monitoring.
- Maintain Regulatory documents of all Participating Institutions.
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc).
- Maintain documentation of all communications.
- Ensure that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP).

2.3 DF/HCC Quality Assurance Office for Clinical Trials (QACT)

In addition to the Coordinating Center, the DF/HCC QACT provides the following support services to assist the DF/HCC Sponsor:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide a central participant registration, which includes review of consent and eligibility.
- Provide auditing services (funding and QACT approval required).

2.4 Participating Institution

Each Participating Institution is expected to comply with all applicable Federal Regulations and DF/HCC requirements, the protocol and HIPAA requirements. All Participating Institutions will provide a list of personnel assigned to the role for oversight of data management at their site to the Coordinating Center.

The general responsibilities for each Participating Institution are as follows:

- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder in accordance with DF/HCC requirements.
- Provide the Coordinating Center with regulatory documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as needed (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.

- Secure and store investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- For protocols using investigational agents, the Participating Institution will order their own investigational agents regardless of the supplier (i.e. National Cancer Institute (NCI), pharmaceutical company).

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

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

3.1 Protocol Distribution

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

3.2 Protocol Revisions and Closures

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

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

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

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

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA

authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB.

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

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Approval letter of the Participating Institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution's IRB
- Participating IRB's approval for all amendments

It is the Participating Institution's responsibility to notify its IRB of protocol amendments. Participating Institutions will have 90 days from receipt to provide the Coordinating Center their IRB approval for amendments to a protocol.

3.5 IRB Re-Approval

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

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

3.6 Participant Confidentiality and Authorization Statement

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

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an Authorization. This Authorization may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide a consent template, which covered entities (Participating Institutions) must use.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per NCI requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number (as described below) and DF/HCC protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

Refer to section 4.4 of the protocol for the participant registration process.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the Participating Institution receives a faxed or e-mailed copy of the participant's registration confirmation memo from the Coordinating Center. Therapy must be initiated per protocol guidelines. The DF/HCC Sponsor and DFCI IRB must be notified of any exceptions to this policy.

3.7.3 Eligibility Exceptions

CTEP specifically prohibits registration of a participant on any NCI Sponsored protocol that does not fully and completely meet all eligibility requirements. The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

3.7.4 Verification of Registration, Dose Levels, and Arm Designation

A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be emailed to the registering institution within one business day of the registration.
Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

3.8 DF/HCC Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and correspondence, and correspondence with the Coordinating Center.

3.9 Protocol Deviations, Exceptions and Violations

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

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

3.9.1 Definitions

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

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

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

3.9.2 Reporting Procedures

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

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

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

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

3.10 Safety Assessments and Toxicity Monitoring

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

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the

protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

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

3.10.1 Guidelines for Reporting Serious Adverse Events

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

Participating Institutions must report the AEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB SAE Reporting Requirements.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Investigators will review any distributed AE reports, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

3.10.2 Guidelines for Processing IND Safety Reports

FDA regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any adverse experience associated with the use of the investigational agent that is both serious and unexpected. The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. The Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.11 Data Management

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

3.11.1 Data Forms Review

When data forms arrive at the DF/HCC QACT, they are reviewed for completeness, protocol treatment compliance, adverse events (toxicities) and response. Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

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

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of four times a year.

4.0 REQUISITIONING STUDY DRUG

The ordering of Palbociclib is specified in protocol Section 8.1.8.

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

Ensure that the pharmacy will be able to receive and store Palbociclib according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., Pfizer) so that any regulatory responsibilities can be met in a timely fashion.

5.0 MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality control oversight for the DF/HCC Multi-center Protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Also, the Participating Institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution or designee.

The DF/HCC Lead Institution will implement on-site as well as virtual monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. At a minimum, the DF/HCC Lead Institute, or designee, will monitor each participating site on an ongoing basis while patients are receiving treatment. Should a Participating Institution be monitored once and then not accrue any additional patients or participant visits, then a second monitoring visit may not be necessary.
Monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management. Additionally, regular and ongoing communication with Participating Institutions, will be accomplished by holding all site teleconferences. The Lead Institution will keep in close touch with the Participating Institutions via email and phone. Source documents from Participating Institutions, will be collected at specific data points that support the primary and or secondary endpoints.

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for

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

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

The Overall PI, or designee, will review all monitoring reports for on-site and virtual monitoring of Participating Institutions to ensure protocol compliance and ability to fulfill responsibilities of participation in the study. The Coordinating Center may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the Coordinating Center.

In addition to monitoring performed by the Coordinating Center, DF/HCC QACT may monitor data for timeliness of submission, completeness, and adherence to protocol requirements. The Lead Institution or designee and, if applicable, QACT Data Analysts assigned to the Protocol will perform the ongoing protocol data compliance monitoring with the support of the Participating Institution's Coordinators, the Principal Investigators, and the Protocol Chair.

5.2 Evaluation of Participating Institution Performance

5.2.1 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and virtual monitoring of Participating Institutions to ensure protocol compliance and ability to fulfill responsibilities of participating in the study. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.2.2 Accrual of Eligible Participants:

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

A minimum of 3 participants per site annually is recommended for Phase II trials. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site.

6.0 AUDITING: QUALITY ASSURANCE

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

6.1 NCI Sponsored Trials

Not applicable.

6.2 DF/HCC Sponsored Trials

One on-site audit will be scheduled by the QACT, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.3 Participating Institution

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

6.4 DF/HCC Sponsor and Coordinating Center

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

6.5 Sub-Standard Performance

The DF/HCC Sponsor, DFCI IRB and the NCI for CTEP trials, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.5.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and compliance with state and federal regulations, will be recommended for a six-month probation period. Such institutions must respond with a corrective action

plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation.

APPENDIX H: PFIZER SAE FAX COVER SHEET

CLINICAL AND MEDICAL CONTROLLED DOCUMENT (CMCD)
REQUIRED FORM – REPORTABLE EVENT FAX COVER SHEET (US)

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		
PRODUCT	Palbociclib (PD0332991)	
PFIZER REFERENCE NUMBER	WI180528	EXTERNAL REFERENCE NUMBER
STUDY TITLE	A Phase II Pilot Feasibility Study of Adjuvant Endocrine Therapy and Palbociclib for High Risk Hormone Receptor Positive Breast Cancer	
PATIENT NUMBER		
INVESTIGATOR	Erica Mayer, M.D., MPH	

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

APPENDIX I: QOL ASSESSMENT

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4

15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent