Cover Page for Clinical Trials Document posting

Official Title: S1400C, “A Phase II Study of Palbociclib for Previously Treated Cell Cycle Gene Alteration Positive Patients with Stage IV Squamous Cell Lung Cancer (Lung-MAP Sub-Study)”

NCT Number: 02785939

Version Date: 9/1/2017

Description:

S1400 [NCT 02154490] is the parent study to **S1400C** [NCT 02785939].

The **S1400** Lung-MAP study is considered one study under one IND consisting of:

- S1400 Version Control Protocol
- S1400 Main Screening Protocol Component
- Multiple Sub-Studies (or sub-protocols) Components

Each component is contained in its own separate document.

S1400C is one of these components. Each “component” consists of the protocol document and its associated informed consent document(s). Since each screening and sub-study component operates independently from the other components contained in Lung-MAP, each has its own version date and NCT number. This is due to the complexity of the study and how it must be entered into different computer programs.

S1400C: CDK4/6 – Palbociclib

A BIOMARKER-DRIVEN MASTER PROTOCOL FOR PREVIOUSLY TREATED SQUAMOUS CELL LUNG CANCER

A PHASE II STUDYOF PALBOCICLIB FOR PREVIOUSLY TREATED CELL CYCLE GENE ALTERATION POSITIVE PATIENTS WITH STAGE IV SQUAMOUS CELL LUNG CANCER (LUNG-MAP SUB-STUDY)

NCT #02154490

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STUDY AGENTS:

Available from Pharmaceutical Collaborators:
Palbociclib (PD-0332991) (NSC 772256) (IND-119672)

Available from Commercial Sources:
Docetaxel * (Taxotere®) (RP56976) (NSC 628503)

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* Docetaxel is not a current study agent effective 12/18/2015.

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available to the SWOG Workbench. Access this by using your active CTEP-IAM USER ID and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

CTSU sites should follow procedures outlined in the protocol for Site Registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.

For patient eligibility questions contact the SWOG Data Operations Center by phone or email:

206-652-2267
S1400question@crab.org

For treatment or toxicity related questions contact S1400CMedicalquery@swog.org.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line:
888-823-5923
ctsucontact@westat.com

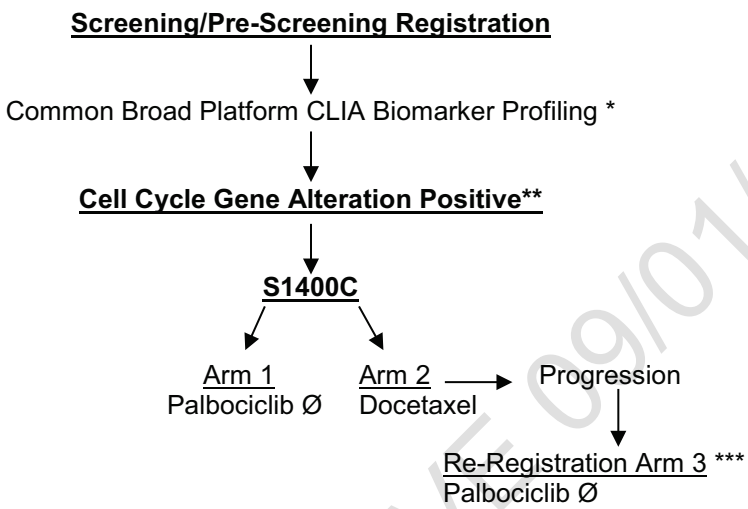
All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Web site is located at https://www.ctsu.org

SCHEMA

OLD SCHEMA

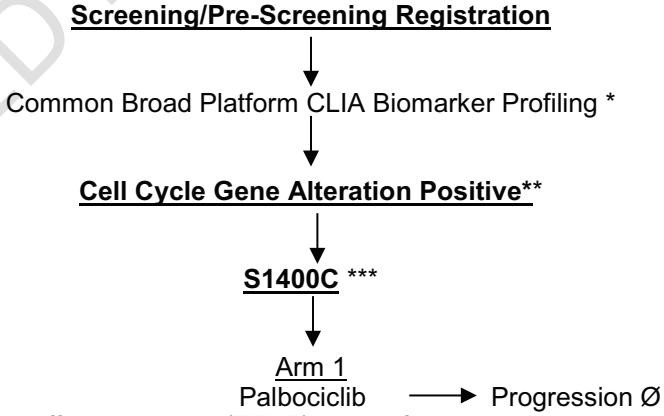
Patients registered prior to Revision #3



* Archival formalin-fixed paraffin-embedded (FFPE) tumor, fresh core needle biopsy if needed
** Notification of sub-study assignment will be provided by the SWOG statistical center (see Section 11.0 in **S1400** for details).
*** Optional re-registration to Arm 3- Palbociclib, (patients must have progressed as defined in Section 10.2d of **S1400**).
Ø Upon progression (as defined in Section 10.2d in **S1400**), patients may be eligible for another sub-study. The new sub-study assignment will be determined by the SWOG Statistical Center. (see Section 14.4).

NEW SCHEMA

Patients registered after Revision #3



* Archival formalin-fixed paraffin-embedded (FFPE) tumor, fresh core needle biopsy if needed
** Notification of sub-study assignment will be provided by the SWOG statistical center (see Section 11.0 in **S1400** for details).
*** Arm 2 Docetaxel has been removed from the Schema as it is closed to accrual per Revision #3, Version Date 11/18/15.
Ø Upon progression (as defined in Section 10.2d in **S1400**), patients may be eligible for another sub-study. The new sub-study assignment will be determined by the SWOG Statistical Center. (see Section 14.4).

1.0 OBJECTIVES

Included here are the objectives related to the single arm Phase II portion of Design #2 (Sequential Phase II to Phase III) as described in **S1400**.

1.1 Primary Objectives

a. Phase II Component

The primary objective within the Phase II component of **S1400C** is to evaluate if there is sufficient evidence to continue to the Phase III component by evaluating the objective response rate (ORR) for cell cycle gene alteration positive patients registered to **S1400C** treated with palbociclib.

b. Phase III Component

If the study meets the criteria specified in **S1400** Section 11.2a, the study will be amended to include a follow-on randomized Phase III trial.

1.2 Secondary Objectives

a. Phase II Component

1. To evaluate investigator-assessed progression-free survival (IA-PFS) and overall survival (OS) of cell cycle gene alteration-positive patients treated with palbociclib.

2. To evaluate the duration of response (DoR) among cell cycle gene alteration positive patients treated with palbociclib who achieve a CR or PR (confirmed and unconfirmed) by RECIST 1.1.

3. To evaluate the frequency and severity of toxicities associated with Palbociclib.

1.3 Translational Medicine Objectives

a. To identify additional predictive tumor/blood biomarkers that may modify response or define resistance to the palbociclib beyond the chosen biomarker for biomarker-driven sub-studies.

b. To identify potential resistance biomarkers at disease progression.

c. To establish a tissue/ blood repository from patients with refractory squamous cell carcinoma (SCCA) of the lung.

2.0 BACKGROUND

The cyclin-dependent kinases (CDKs) form heterodimeric protein complexes with cyclins and play key roles in cell cycle progression and transcription regulation. In malignant cells, increased expression of cyclins in conjunction with loss of function of endogenous CDK inhibitors results in the selective growth advantage characteristic of human cancer. *(1)*

Cyclin D1 amplification

In a variety of tumor types, cyclin D family members (D1, D2 and D3) have been found to be overexpressed, leading to hyperactivation of CDKs 4 and 6 and uncontrolled activation of the cell cycle. Increased expression may be secondary to amplification, translocation or overexpression of

the genes that encode D-type cyclins. Amplification of the gene encoding cyclin D1 may occur in breast, lung, esophageal and head and neck cancers, and the use of a CDK4/6 inhibitor may represent a successful treatment strategy for CCND1-amplified subsets of these tumor types.

Overexpression of cyclin D1 in breast cancer tumor samples has been well established. *(2)* Amplification of the cyclin D1 gene (CCND1) has been found in 15-20% of breast cancer tumor samples with overexpression of the protein seen in approximately 33% of samples overall. *(3,4)* In some cases, this overexpression of cyclin D1 is secondary to estrogen receptor (ER) stimulation and is the basis for the randomized Phase II trial evaluating the combination of the CDK4/6 inhibitor palbociclib and letrozole; this trial demonstrated a substantial survival benefit for the combination compared to the single agent letrozole alone (26.2 months vs. 7.5 months, HR=0.37, p<0.001). *(5,6,7)*

Squamous cell carcinoma of the lung has been demonstrated to have CCND1 alterations. In squamous cell carcinomas, CCND1 was found to be amplified in a number of tumors evaluated, including squamous non-small cell lung cancer. In the Cancer Genome Atlas (TCGA) data CCND1 amplification was seen in 12% of squamous cell carcinoma, although the latter often occur in association with other abnormalities of the CDK4/Rb pathway. In addition, many of these amplifications were associated with loss of INK4, contributing to further disruption of the cyclin D-CDK4/6-Rb-INK4 axis. Although Rb loss was detected in some of the analyzed specimens, they did not overlap with CCND1 amplifications. *(8)*

CDK4 Amplification

CDK4/6 amplifications have also been identified in squamous cell carcinomas of the lung and esophagus, glioblastoma multiforme and liposarcomas. *(9,10)*

Well differentiated/dedifferentiated liposarcoma (WDLD/DDLS) is the paradigm malignancy characterized by CDK4 amplification and palbociclib has demonstrated growth inhibition in WDLS/DDLS cells in vitro and in xenograft models. Proof of principle that targeting CDK4 amplified cancer with palbociclib can be therapeutically important was established in a Phase II trial of palbociclib in WDLS/DDLS. All patients had received at least one previous line of therapy. Primary end-point was 12 week progression free survival (PFS): on the basis of historical data a PFS > 40% at this point was considered promising. In 29 evaluable patients the 12 week PFS was 66% and median PFS 17.9 weeks. One patient responded and three others had a decrease in tumor size of greater than 10%. These responses were very gradual occurring over many months.

CDK4 amplification in squamous non-small cell lung cancer (NSCLC) occurs as a relatively rare event with little other evidence of accompanying gene rearrangement as analyzed by comparative genomic hybridization (CGH). It is expected that about 1% of squamous NSCLC will have a CDK4 amplification. However, it seems that these might be high level/high copy number amplifications and are associated with increased CDK4 message and protein expression.

Palbociclib Dose Rationale and Summary of Clinical Experience

Palbociclib has been tested in a Phase I 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 treatment emergent adverse events (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 two dosing schedules, both during and after Cycle 1. One partial response 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 was selected for further clinical development and the recommended Phase II dose for this schedule was determined to be 125 mg/d. Therefore palbociclib will be administered at a dose of 125 mg PO daily on Day 1 to Day 21 following a 1 week of rest period, given as 4 weeks cycles.

3.0 DRUG INFORMATION

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this sub-study, palbociclib is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Palbociclib (PD-0332991) (NSC 772256) (IND-119672)

a. PHARMACOLOGY

Mechanism of Action: Palbociclib, an orally active pyridopyrimidine, is a potent and highly selective reversible inhibitor of cyclin-dependent kinase (CDK) 4 and CDK6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated in laboratory models and early clinical trials. Palbociclib preclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytoreductive activity. Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific retinoblastoma (Rb) phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of Rb. Consequently, the phosphorylation status of these sites serves as specific biomarkers of CDK4/6 inhibition.

b. PHARMACOKINETICS

1. Absorption:

Pharmacokinetic parameters are available from all 74 patients enrolled in Protocol A5481001 following a single-dose (Day 1 of Cycle 1), and from 51 patients following multiple-dose administration (Day 8 of Cycle 1) of daily doses ranging from 25 to 225 mg of palbociclib. In addition, PK parameters are also available for nine patients on Day 14 of Cycle 1 (from patients on Schedule 2/1) and four patients on Day 21 of Cycle 1 (from patients on Schedule 3/1). On Day 1, all patients had detectable plasma concentrations of palbociclib at the first measured time point (1 hour) following oral administration. The exposure (AUC(0-10) and Cmax) increased in a dose-proportional manner over the dose range of 25-225 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 Tmax of ~4 hours.

Preliminary results from the recently performed food effect study, A5481021, in healthy volunteers suggest that the administration of palbociclib with food results in more consistent drug uptake and exposure than administration of palbociclib in a fasted state. As a result of these findings, patients should take palbociclib with food.

2. Distribution:

In Protocol A5481001 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.

3. Metabolism:

Data is available from 6 healthy males subjects in Protocol A5481011 to describe the mass balance and metabolic fate of single oral doses of palbociclib. Subjects were administered single oral 125 mg doses of palbociclib. Palbociclib was well absorbed and extensively metabolized. In humans, the primary routes of metabolic clearance include multiple oxidative pathways and a single conjugative pathway (sulfonation). Minor primary routes of metabolism include glucuronidation and acylation (acetylation and formylation) pathways. Greater than 50% of the clearance mechanism can be assigned to oxidative pathways, while primary conjugative processes, (sulfonation and glucuronidation), contribute approximately 26% and 2%, respectively, to the overall clearance, with acylation (formyl and acetyl) pathways contributing less than 3%. Direct excretion of unchanged drug in the urine and feces was found to be minimal. The sulfamic acid of palbociclib was the predominant metabolite excreted in the feces for all subjects, accounting for 26% of the administered dose on average. Unchanged palbociclib and multiple isomeric monohydroxylated metabolites were the major recovered urinary components of the dose, accounting for 3.7 % and 3.5 % of the administered dose on average, respectively. Plasma samples were pooled across time points and subjects to yield a single sample representative of a mean 0-120 hr AUC. In circulation, palbociclib and the glucuronide conjugate of palbociclib were the primary drug-related materials, accounting for 23% and 15%, respectively.

4. Elimination:

In Protocol A5481001 renal excretion of palbociclib was a minor route of elimination with ~1.7% of the drug excreted unchanged in urine over the 10-hour collection period in the 125 mg and 200 mg dose group, combined. The mean renal clearance (CLR) was 6.59 L/hour.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 759 patients. Below is the CAEPR for Palbociclib (PD-0332991).

Version 2.2, April 1, 20161

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 4.0 Term) [n= 759]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
		Febrile neutropenia
EYE DISORDERS		
	Dry eye	
	Watering eyes	
GASTROINTESTINAL DISORDERS		
	Constipation	
	Diarrhea	
	Mucositis oral	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever	
INFECTIONS AND INFESTATIONS		
Infection[2]		
INVESTIGATIONS		
	Lymphocyte count decreased	
Neutrophil count decreased		
Platelet count decreased		
White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
NERVOUS SYSTEM DISORDERS		
	Dysgeusia	
	Headache[3]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Epistaxis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Dry skin	
	Skin and subcutaneous tissue disorders - Other (rash)[4]	
VASCULAR DISORDERS		
		Thromboembolic event

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.
[3] Headache has been observed in trials using Palbociclib (PD-0332991) in combination with fuvestrant.
[4] Rash includes rash, rash maculo-papular, erythema, erythematous rash, erysipelas, rash pruritic, rash papular, generalized rash, exanthema, allergic dermatitis, dermatitis acneiform, dermatitis, and palmar-plantar erythrodysesthesia syndrome.
[5] Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC.

Adverse events reported on Palbociclib (PD-0332991) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Palbociclib (PD-0332991) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Palpitations; Pericarditis; Sinus bradycardia; Supraventricular tachycardia
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (retinal hemorrhage)
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Esophageal stenosis; Flatulence; Gastric hemorrhage; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (large intestine perforation); Gastrointestinal disorders - Other (oropharyngeal pain); Intra-abdominal hemorrhage; Lower gastrointestinal hemorrhage; Small intestinal obstruction; Small intestinal perforation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Localized edema; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice)
IMMUNE SYSTEM DISORDERS - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Creatinine increased; GGT increased; INR increased; Investigations - Other (pancytopenia); Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Flank pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (osteomyelitis); Musculoskeletal and connective tissue disorder - Other (osteonecrosis); Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysphasia; Intracranial hemorrhage; Nervous system disorders - Other (peripheral neuropathy)[5]; Syncope

PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Pleural effusion; Pneumonitis; Postnasal drip; Pulmonary edema; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Pruritus
VASCULAR DISORDERS - Hypertension; Hypotension

Note: Palbociclib (PD-0332991) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Data from pre-clinical studies has indicated that palbociclib has the potential to delay cardiac repolarization as measured by prolongation of the QT interval on ECG. In vitro (hERG) and in vivo (dog telemetry) studies revealed a potential for QT prolongation at unbound concentrations ≥ 14 fold the unbound steady state Cmax associated with the clinical dose of 125 mg QD. A preliminary pharmacokinetic/pharmacodynamic analysis has been conducted to explore the QT/QTc and plasma PD 032991 concentration relationship for Study A5481001 (FIH study) by using graphical methods and mixed effects linear modeling (NONMEM). Data from 73 patients were used for the analysis, and no patient had a maximum on treatment QTcF value of ≥ 500 msec. The QTcF changes from the baseline at the mean Cmax calculated for 200 mg dose were simulated for 10,000 patients. The mean and upper 95% confidence interval of QTcF change from the baseline were 5.8 and 9.4 msec, respectively.

2. Pregnancy and Lactation: Fertility and teratology studies with palbociclib have not been conducted; therefore, safety for pregnant women of childbearing capacity and for the fetus cannot be implied from the existing data. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

Palbociclib caused testicular degeneration in rats and dogs. The incidence and severity was dose related and correlated with decreases in testicular weight in the rat. Testicular degeneration was not reversed after cessation of treatment and progressed in severity in both species. Testicular degeneration produced by palbociclib is consistent with Cdk inhibition and alterations in cell cycle kinetics.

Women of childbearing potential must have a negative pregnancy test prior to treatment with palbociclib. Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraceptive during the period of the trial and for at least 90 days after completion of treatment. Male patients must be surgically sterile or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment. The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.

Even though there may not be an associated SAE, exposure to palbociclib during pregnancy or lactation is reportable.

If a patient is suspected to be pregnant, all study drugs should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, she may resume dosing.

If a patient is found to be pregnant, the study drug will be discontinued immediately. The patient will be followed for adverse events through the end of this pregnancy. Future treatment decisions are at the discretion of the patient's treating physician.

No studies with palbociclib have been conducted in humans to assess the effect on milk production, presence in breast milk or effects on a breast-fed child. Excretion of palbociclib in human milk is unknown.

3. Drug Interactions:

In vitro data indicate palbociclib is primarily metabolized by CYP3A4.

CYP3A Inhibitors
Concomitant administration of agents known to inhibit CYP3A isoenzymes (eg, ketoconazole, miconazole, itraconazole, posaconazole, clarithromycin, erythromycin, tilithromycin, nefazodone, diltiazem, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, and grapefruit juice) may increase palbociclib exposure and thus are not recommended.

CYP3A Inducers
Concomitant administration of agents that are strong CYP3A inducers (such as phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, and St. John's Wort) may reduce the exposure of palbociclib and thus are also not recommended. In A5481004, palbociclib was administered in combination with dexamethasone. Dexamethasone is a known inducer of CYP3A4. The exposure of palbociclib observed from A5481004 was considerably lower compared to exposures observed in studies A5481001 (single agent) or A5481003 (in combination with letrozole) likely due to the induction effect of dexamethasone.

Time Dependent Inhibition of CYP3A
Based on in vitro studies (human liver microsomes and human hepatocytes), palbociclib has a low potential to produce drug interactions through inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 (IC50 values all > 30 μM) and by inducing CYP3A4 and CYP1A2 activity. In vitro, palbociclib demonstrated time-dependent inhibition of CYP3A in human liver microsomes. In vivo, inactivation of CYP3A by palbociclib may result in drug interactions with compounds that are predominantly metabolized by this enzyme. Therefore, caution must be exercised in patients receiving palbociclib in combination with drugs that are predominantly metabolized by CYP3A. In particular, co-administration of palbociclib with CYP3A4 substrates with narrow therapeutic indices (e.g., astemizole, terfenadine, cisapride, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, alfentanil and fentanyl, excluding transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine) must be avoided. Preliminary pharmacokinetic data are available from a midazolam drug-drug interaction study. Midazolam is a sensitive CYP3A4/5 probe substrate. When midazolam was coadministered with palbociclib, median plasma midazolam concentrations were slightly higher than with midazolam alone. This is consistent with a weak time-dependent CYP3A inhibition mediated by palbociclib.

In vitro studies with P-glycoprotein
In vitro evaluation of the potential for palbociclib to inhibit the drug efflux transporter P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) was conducted in trasfected cells. Palbociclib is a weak inhibitor of both P-gp and BCRP. The potential of palbociclib to inhibit P-gp and BCRP in the GI tract was also assessed. The risk for GI interactions with P-gp and BCRP is considered to be low at the clinically-relevant dose.

d. DOSING & ADMINISTRATION

1. Dosing: See **S1400C** Section 7.0, Treatment Plan.

2. Administration Instructions: Palbociclib is administered orally. Patients should be instructed to swallow palbociclib capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day. Patients should be instructed to record daily administration of the study drugs in a patient diary. Patients should take palbociclib with food. Patients experiencing investigational product related toxicity may have their dose modified according to Section 8.0). Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day. Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed. Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose.

e. HOW SUPPLIED

1. For this study, palbociclib is considered an investigational agent and will be supplied free of charge for this protocol by Pfizer, Inc.

2. Formulation and dose form available: Palbociclib is supplied as capsules containing 125 mg, 100 mg or 75 mg of palbociclib. The capsules can be differentiated by their size and color (see below). The capsules will be supplied in HDPE bottles commercially labeled that contain 21 capsules each.

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

f. STORAGE, PREPARATION & STABILITY

Palbociclib capsules should be stored at controlled room temperature (15-30ºC) in their original container.

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.

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 guidelines 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. Returned unused medication MUST NOT be re-dispensed to patient.

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 one 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.

g. DRUG ORDERING & ACCOUNTABILITY

1. Supplied by Pfizer and distributed by the CTEP, DCTD, NCI.

Drug ordering: Study specific supplies will be provided to sites once a patient has been randomized. Starter supplies will not be provided. NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (**S1400C**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime. For palbociclib, use of the NCI Oral DARF is mandatory.

2. Drug Handling and Accountability

a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Drug

Accountability Record Form available on the NCI home page (http://ctep.cancer.gov). For palbociclib, use of the oral DARF is mandatory.

b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug Return and/or Disposition Instruction

a. All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

b. Drug expiration: Stability testing is ongoing. PMB will send a stock recovery letter when notified that the agent is no longer suitable for use.

4. Contact Information

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

4.0 STAGING CRITERIA

See Section 4.0 of **S1400** for staging criteria.

5.0 ELIGIBILITY CRITERIA

Patient must meet the eligibility criteria in Section 5.0 of **S1400C** to be eligible for **S1400C**. If the patient does not meet the sub-study specific eligibility criteria listed in Section 5.1 and Section 5.2 of **S1400C**, but meets the common sub-study criteria listed in Section 5.3 of **S1400C**, submit the **S1400** Request for Sub-Study Reassignment Form for sub-study reassignment. Patients on Arm2, docetaxel, that have progressed and are proceeding to Re-Registration must meet the eligibility criteria in Section 5.4 of **S1400C** to be eligible. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at S1400question@crab.org prior to registration.

5.1 Sub-Study Specific Disease Related Criteria

a. Patients must be assigned to **S1400C**. **S1400C** biomarker eligibility defined as Cell Cycle Gene Alteration Positive as follows:

Gene	Alteration type	Eligible alteration *
CDK4	Substitution	None
	Fusion	None
	Amplification	FMI standard thresholds: ≥ 6 estimated copies (or ≥ 7 in triploid, ≥ 8 in tetraploid+ samples)
CCND1	Substitution	None
	Fusion	None
	Amplification	FMI standard thresholds: ≥ 6 estimated copies (or ≥ 7 in triploid, ≥ 8 in tetraploid+ samples)

CCND2	Substitution	None
	Fusion	None
	Amplification	FMI standard thresholds: ≥ 6 estimated copies (or ≥ 7 in triploid, ≥ 8 in tetraploid+ samples)
CCND3	Substitution	None
	Fusion	None
	Amplification	FMI standard thresholds: ≥ 6 estimated copies (or ≥ 7 in triploid, ≥ 8 in tetraploid+ samples)

*Note: Patients must have at least one of the listed alterations.

5.2 Sub-Study Specific Clinical/Laboratory Criteria

a Patients must not be taking within 7 days prior to sub-study registration, nor plan to take while on protocol treatment and for 14 days after the last dose of study treatment, strong CYP3A4 inhibitors and/or strong CYP3A4 inducers. Moderate inhibitors or inducers of isoenzyme CYP3A4 should be avoided, but if necessary can be used with caution (see Section 7.2).

b. Patients must not be taking within 7 days prior to sub-study registration, nor plan to take while on protocol treatment, drugs that are known to prolong the QT interval. See https://www.crediblemeds.org/index.php).

c. Patients must not have a screening QTcF interval > 480 msec based on the average of triplicate EKGs performed within 28 days prior to registration. NOTE: Triplicate EKGs are required at other timepoints (see Section 9.0). Patients must not have any family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes.

d. Patients must be able to take oral medications. Patient may not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of palbociclib (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).

e. Patients must have a Na, K, Cl, Ca, Mg, and HbA1c performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar.

f. Patients must also be offered participation in banking for future use of specimens as described in Section 15.0.

5.3 Common Eligibility Criteria for all Sub-Studies

The **S1400** Common Eligibility Criteria have been incorporated into Section 5.0 of each sub-study for ease of reference.

a. Patients whose biomarker profiling results indicate the presence of an EGFR mutation or EML4/ALK fusion are not eligible. Due to existence of approved therapies the biomarker exclusion rules are as follows:

Gene	Alteration type	Ineligible Alteration
EGFR	Substitution	L858R, T790M, A289V, G719A, S768I, G719C, R108K, G598V, R222C, L62R, L861Q, P596L, V774M

	Indel	non-frame shifting insertions or deletions between amino acids 740 and 780, in exons 19 and 20, transcript NM_005228
	Fusion	None
	Amplification	None
ALK	Substitution	None
	Indel	None
	Fusion	EML4-ALK, CLIP4-ALK, CLTC-ALK, KIF5B-ALK, NPM1-ALK, RANB2-ALK, STRN-ALK, TFG-ALK
	Amplification	None

b. Patients must have progressed (in the opinion of the treating investigator) following the most recent line of therapy.

c. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study registration. Patients must have recovered (≤ Grade 1) from any side effects of prior therapy. Patients must not have received any radiation therapy within 14 days prior to sub-study registration. (See 5.3 for criteria regarding therapy for CNS metastases).

d. Patients must have measurable disease (see Section 10.0) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in Section 10.0. Measurable disease must be assessed within 28 days prior to sub-study registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to sub-study registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to registration. See Sections 15.0 and 18.1 for guidelines and submission instructions for required central radiology review.

e. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment and prior to registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.

f. Patient must have fully recovered from the effects of surgery at least 14 days prior to sub-study registration.

g. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

h. Patients must have an ANC ≥ 1,500/mcl, platelet count ≥ 100,000 mcl, and hemoglobin ≥ 9 g/dL obtained within 28 days prior to sub-study registration.

i. Patients must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and either ALT or AST ≤ 2 x IULN within 28 days prior to sub-study registration (if both ALT and AST are done, both must be ≤ 2 IULN). For patients with liver metastases, bilirubin and either ALT or AST must be ≤ 5 x IULN (if both ALT and AST are done, both must be ≤ 5 x IULN).

j. Patients must have a serum creatinine ≤ the IULN OR measured or calculated creatinine clearance ≥ 50 cc/min using the following Cockroft-Gault Formula:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{actual body weight in kg})\ \dagger}{72 \times \text{serum creatinine}}$$

Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 28 days prior to sub-study registration.
†The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
*Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

k. Patients must have Zubrod performance status of 0-1 (see Section 10.4) documented within 28 days prior to sub-study registration.

l. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see Section 18.1b).

m. Patients must not have documented evidence of acute hepatitis or have an active or uncontrolled infection.

n. Patients with a known history of HIV seropositivity:

1. Must have undetectable viral load using standard HIV assays in clinical practice.
2. Must have CD4 count ≥ 400/mcL.
3. Must not require prophylaxis for any opportunistic infections (i.e., fungal, mAC, or PCP prophylaxis).
4. Must not be newly diagnosed within 12 months prior to sub-study registration.

o. Prestudy history and physical exam must be obtained within 28 days prior to sub-study registration.

p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

q. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures

outlined in the protocol, he/she is responsible for beginning contraceptive measures.

r. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

s. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).

t. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

5.4 Step 2 Palbociclib Re-Registration

a. Patients must have progressed (as defined in Section 10.2d in **S1400**) on Arm 2 (docetaxel) of this sub-study.

b. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to Step 2 Re-Registration. Patients must have recovered (< Grade 1) from any side effects of prior therapy.

c. Patients must have measurable disease (see Section 10.1) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in Section 10.1c. Measurable disease must be assessed within 28 days prior to Step 2 Re-Registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to Step 2 Re-Registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to registration. See Sections 15.0 and 18.1c for guidelines and submission instructions for required central radiology review.

d. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to Step 2 Re-Registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment and prior to re-registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to re-registration.

e. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

f. Patients must not have a screening QTcF interval > 480 msec based on the average of triplicate EKGs performed within 28 days prior to Step 2 Re-Registration. NOTE: Triplicate EKGs are required at other timepoints (see Section 9.0). Patients must not have any family or personal history of long or short QT

syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes.

g. Patients must have an ANC ≥ 1,500/mcl, platelet count ≥ 100,000 mcl, and hemoglobin ≥ 9 g/dL obtained within 28 days prior to Step 2 Re-Registration.

h. Patients must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and either ALT or AST ≤ 2 x IULN within 28 days prior to Step 2 Re-Registration (if both ALT and AST are done, both must be < 2 IULN). For patients with liver metastases, bilirubin and either ALT or AST must be ≤ 5 x IULN (if both ALT and AST are done, both must be ≤ 5 x IULN).

i. Patients must have a serum creatinine ≤ the IULN OR measured or calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-Gault Formula:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{actual body weight in kg})\ \dagger}{72 \times \text{serum creatinine}^*}$$

Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 28 days prior to Step 2 Re-Registration.

† The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

j. Patients must have a Na, K, Cl, Ca, Mg, and HbA1c performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar.

k. Patients must have Zubrod performance status of 0-1 (see Section 10.4) documented within 28 days prior to Step 2 Re-Registration.

l. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see Section 18.1b).

m. Patients must not have documented evidence of acute hepatitis or have an active or uncontrolled infection.

n. Patients with a known history of HIV seropositivity:

1. Must have undetectable viral load using standard HIV assays in clinical practice.
2. Must have CD4 count ≥ 400/mcL.
3. Must not require prophylaxis for any opportunistic infections (i.e., fungal, mAC, or PCP prophylaxis).
4. Must not be newly diagnosed within 12 months prior to re-registration.

o. Prestudy history and physical exam must be obtained within 28 days prior to re-registration.

p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

q. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

r. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

s. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).

t. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

6.0 STRATIFICATION FACTORS

Prior to Revision #3, (Version Date 11/18/15) patients were stratified as follows below. As the design and objectives have been modified to a Single arm Phase II, followed by a Randomized Phase III, randomization and stratification are not required for the Phase II component.

6.1 Patients were randomized between palbociclib and docetaxel using block randomization.

6.2 Randomization was stratified by:

a. Zubrod Performance Status (0-1 vs. 2)

b. Gender (Male vs. Female)

c. Number of prior therapies (1 vs. 2 or more).

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Drs. Martin J. Edelman and Kathy S. Albain at S1400CMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication and Supportive Care

Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

Patients randomized to docetaxel should pre-medicate with dexamethasone beginning 24 hours prior to docetaxel administration. Dexamethasone may be administered per local institutional guidelines. Recommended dose listed below.

7.2 Treatment – **S1400C**

Prior to Revision #3, (Version Date 11/18/15) patients were randomized into one of two treatment arms. As the design and objectives have been modified to a Single arm Phase II, followed by a Randomized Phase III, all patients will be placed into Arm 1: Palbociclib for the Phase II portion. This section will be amended should the trial continue with the Randomized Phase III portion. The information regarding the docetaxel treatment plan will remain within the section for the patients continuing to receive treatment per protocol. Patients currently on Arm 2, docetaxel will be given the option to re-register to Arm 3, palbociclib after progressing as defined **S1400** Section 10.2d.

a. **Arm 1: Palbociclib**

Agent	Dose	Route	Day	Schedule*
Palbociclib	125 mg	Oral	1-21	21 days on/ 7 days off

* NOTE: A cycle of treatment is 28 days. Disease assessment must occur every 6 weeks. Treatment will continue until any of the criteria in Section 7.4 is met.

Patients should take palbociclib with food. Palbociclib will be administered orally once a day for 21 days (followed by 7 days off treatment) of every 28-day cycle.

Patients should be instructed to swallow palbociclib capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day.

Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.

Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.

Patients who inadvertently take one extra dose during a day must be instructed to skip the next day's dose.

Prohibited Medications
The following treatments are prohibited throughout the duration of the active treatment phase:

Strong CYP3A inhibitors/inducers: palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are 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, phenobarbital, phenytoin, primidone,

rifabutin, rifampin, rifapentin, and St. John's wort, are not allowed in the study.

Drugs known to cause QT interval prolongation are prohibited during protocol treatment. (See https://www.crediblemeds.org/index.php.)

Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If usage of the following treatments is deemed necessary, consultation and agreement with the Study Chair is required prior to treatment initiation.

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed. The use of herbal medicine is not recommended during the active treatment phase.

Moderate CYP3A Inducers: The concurrent use of moderate CYP3A inducers such as dexamethasone or omeprazole is not recommended.

CYP3A Substrates: palbociclib and its oxidative metabolite, PF-05089326, demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 enzyme activities and thus, showed low potential for CYP-mediated pharmacokinetic drug interactions. However, palbociclib and PF-05089326 caused time-dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6β hydroxylase activities with Ki and kinact values for palbociclib of 10 μM, 0.036 min-1 and 19 μM, 0.087 min-1 and for PF 05089326 of 7.0 μM, 0.094 min-1 and 6.4 μM, 0.15 min-1, respectively. Therefore, palbociclib and its metabolite may have the potential for pharmacokinetic drug interactions with compounds for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance. While the clinical significance of this inhibitory effect is yet to be investigated, caution must be exercised in patients receiving palbociclib in combination with drugs that are predominantly metabolized by CYP3A. In particular, co-administration of palbociclib with CYP3A4 substrates with narrow therapeutic index including, but not limited to alfentanil, aripiprazole, cyclosporine, ergotamine, fentanyl, halofantrine, pimozide, quinidine, sirolimus, tacrolimus, triazolam, astemizole, cisapride, and terfenadine are not recommended during the active treatment phase of the trial. Alternative therapies should be used when available.

Permitted Medications

The following treatments are permitted throughout the duration of the active treatment phase:

Standard therapies for pre-existing medical conditions, medical and/or surgical complications, and palliation: any medication intended solely for supportive care (eg, analgesics, antidiarrheals, antidepressants) may also be used at the investigator's discretion. All medications should be recorded.

Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors for the treatment of osteoporosis or management of existing bone metastases may be continued for patients who have been receiving them at a stable dose for at least 2 weeks prior to randomization. However the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of patient from the active treatment phase unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the patient's source documentation.

Hematopoietic growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]): Primary prophylactic use of granulocyte-colony stimulating factors is not permitted but they may be used to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guideline. If neutropenic complications are observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered to be a reasonable alternative.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

b. **Arm 2: Docetaxel** (Closed to accrual per Revision #3)

Agent	Dose	Route	Day	Schedule*
Dexamethasone	8 mg BID **	Oral, beginning 24 hours prior to docetaxel	0-2	Q 21 days
Docetaxel	75 mg/m^2	IV	1	Q 21 days

* Note: A cycle of treatment is 21 days. Disease assessment must occur every 6 weeks. Treatment will continue until any of the criteria in Section 7.4 is met.
** Dexamethasone may be administered per local institution guidelines. Recommended dose listed above.

c. **Arm 3: Re-Registration Treatment with Palbociclib**

Upon progression (see Section 10.2d in **S1400**), patients in Arm 2 may be eligible for Re-Registration to receive palbociclib as follows:

Agent	Dose	Route	Day	Schedule*
Palbociclib	125 mg	Oral	1-21	21 days on/ 7 days off

* NOTE: A cycle of treatment is 28 days. Disease assessment must occur every 6 weeks. Treatment will continue until any of the criteria in Section 7.4 is met.

Patients should take palbociclib with food. Palbociclib will be administered orally once a day for 21 days (followed by 7 days off treatment) of every 28-day cycle.

Patients should be instructed to swallow palbociclib capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day

Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.

Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.

Patients who inadvertently take one extra dose during a day must be instructed to skip the next day's dose.

Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

Strong CYP3A inhibitors/inducers: palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are 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, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort, are not allowed in the study.

Drugs known to cause QT interval prolongation are prohibited during protocol treatment. (See https://www.crediblemeds.org/index.php.)

Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If usage of the following treatments is deemed necessary, consultation and agreement with the Study Chair is required prior to treatment initiation.

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed. The use of herbal medicine is not recommended during the active treatment phase.

Moderate CYP3A Inducers: The concurrent use of moderate CYP3A inducers such as dexamethasone or omeprazole is not recommended.

CYP3A Substrates: palbociclib and its oxidative metabolite, PF-05089326, demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 enzyme activities and thus, showed low potential for CYP-mediated pharmacokinetic drug interactions. However, palbociclib and PF-05089326 caused time-dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6β hydroxylase activities with Ki and kinact values for palbociclib of 10 μM, 0.036 min-1 and 19 μM, 0.087 min-1 and for PF 05089326 of 7.0 μM, 0.094 min-1 and 6.4 μM, 0.15 min-1, respectively. Therefore, palbociclib and its metabolite may have the potential for pharmacokinetic drug interactions with compounds for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance. While the clinical significance of this inhibitory effect is yet to be investigated, caution must be exercised in patients receiving palbociclib in combination with drugs that are predominantly metabolized by CYP3A. In particular, co-administration of palbociclib with CYP3A4 substrates with narrow therapeutic index including, but not limited to alfentanil, aripiprazole, cyclosporine, ergotamine, fentanyl, halofantrine, pimozide, quinidine, sirolimus, tacrolimus, triazolam, astemizole, cisapride, and terfenadine are not recommended during the active treatment phase of the trial. Alternative therapies should be used when available.

Permitted Medications

The following treatments are permitted throughout the duration of the active treatment phase:

Standard therapies for pre-existing medical conditions, medical and/or surgical complications, and palliation: any medication intended solely for supportive care (eg, analgesics, antidiarrheals, antidepressants) may also be used at the investigator's discretion. All medications should be recorded.

Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors for the treatment of osteoporosis or management of existing bone metastases may be continued for patients who have been receiving them at a stable dose for at least 2 weeks prior to randomization. However the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of patient from the active treatment phase unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the patient's source documentation.

Hematopoietic growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]): Primary prophylactic use of granulocyte-colony stimulating factors is not permitted but they may be used to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guideline. If neutropenic complications are observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered to be a reasonable alternative.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

7.3 Drug Compliance Documentation

Drug compliance for palbociclib will be recorded by patients on the Intake Calendar (see **S1400** abstract page at www.swog.org). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.4 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Sections 10.2d and 10.2e of **S1400**).*

* Upon progression, the **S1400** Request for New Sub-Study Assignment Form may be submitted to receive a new sub-study assignment (see Section 14.0).

b. Arm 2 (docetaxel) only: If patient has documented progression (as defined in Section 10.2d in **S1400)**, patient may continue to re-registration to receive palbociclib. Patient would then be removed from re-registration protocol treatment upon subsequent progression of disease or symptomatic deterioration (as defined in Section 10.2d or 10.2e in **S1400)**.

c. Unacceptable toxicity.

d. Treatment delay for any reason > 28 days (or as noted in Section 8.0).

e. The patient may withdraw from this study at any time for any reason.

7.5 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.6 Follow-Up Period

Patients will be followed until death or 3 years after sub-study registration, whichever occurs first. Patients registered to Step 2 (Re-Registration) will be followed until death or 3 years after Step 2 Re-Registration. Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. Missed doses for the oral drugs are to be omitted rather than made up.

b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c. Reductions are based on the dose given in the preceding reporting period and are based on toxicities observed since the prior toxicity evaluation.

d. Once dose is reduced, patients will continue at the new dose. No dose re-escalations are allowed.

e. A maximum of two dose reductions are allowed.

8.3 Dose Modifications - Palbociclib

DRUG	DOSE LEVEL	DOSE
Palbociclib	Full	125 mg/d
	-1 Level	100 mg/d
	-2 Level	75 mg/d*

* Palbociclib dose reduction below 75 mg/d is not allowed.

a. General Considerations

1. No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. Investigators may use supportive care measures to manage side effects based on local institutional guidelines.

2. Doses may be held as needed until toxicity resolution up to 28 days. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

3. If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined below. If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

4. In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, non-cancer related surgery) lasting > 2 weeks, treatment resumption will be decided on an individual basis. If treatment is delayed > 28 days for any reason, the patient must be removed from protocol treatment.

5. 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 the following sections. In the event of significant treatment-related toxicity, palbociclib dosing may be interrupted or delayed and/or reduced as described below. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

   Dose modifications may occur in three ways:

   a. Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
   b. Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
   c. In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

6. If the re-treatment parameters are met within 28 days of treatment interruption, palbociclib may be resumed. Please see above for adverse events requiring dose reduction at the time of treatment resumption.

7. If these parameters have not been met after 28 days of treatment interruption (including the scheduled 1 week off treatment), the patient must be removed from protocol treatment (see Section7.4).

b. Dose Modifications

There will be no dose escalations.

Toxicity	**Actions**
Neutropenia	
Grade 3 or 4, uncomplicated	Patients with Grade 3 or 4 neutropenia without fever will have dose held until recovery to ≤ Grade 2. Restart treatment with the same dose.
Grade 3 or 4, complicated	Patients with Grade 3 or 4 neutropenia with documented infection or Grade 2 fever will have dose held until recovery to ≤ Grade 2. Restart treatment with the one dose reduction.
Grade 4	Patients with Grade 4 neutropenia will have dose held until recovery to ≤ Grade 2. Restart treatment with the one dose reduction.

Thrombocytopenia	
Grade 3 or 4	Patients with Grade 3 or 4 will have dose held until recovery to ≤ Grade 2. Restart treatment with the same dose.
Grade 4	Patients with Grade 4 will have dose held until recovery to ≤ Grade 2. Restart treatment with one dose reduction.
Non-hematological Toxicity	
Grade 3 or 4	Patients with Grade 3 or 4 will have dose held until recovery to ≤ Grade 1 or baseline with one dose reduction.
Hepatic Dysfunction	
Grade > 2	Patients experiencing concurrent ≥ Grade 2 AST or ≥ Grade 2 ALT and Grade ≥ 2 bilirubin will have treatment withheld while the cause is investigated. Dose will be held until recovery to ≤ Grade 1. Restart treatment.
QTc Prolongation	
Grade 2, Reversible cause identified	Hold dose and treat reversible cause. Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤ 480 msec Restart treatment at the same dose level.
Grade 2, No reversible cause identified	Hold dose. Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤ 480 msec Restart treatment at the same dose level
Grade 2, continued QTc Prolongation	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.
Grade 3, Reversible cause identified	Hold dose until QTc ≤ 480 msec and potential reversible causes are corrected. Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec If QTc remains above 480msec, a cardiologist should be consulted. Restart treatment at the same dose level.
Grade 3, No reversible cause identified	Hold dose until QTc ≤ 480 msec Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec If QTc remains above 480msec, a cardiologist should be consulted. Restart treatment at one dose reduction.
Grade 3, second QTc Prolongation	If the Grade 3 QTc prolongation occurs again after one dose reduction, further dose adjustment and/or discontinuation should be discussed with study medical monitor in consultation with a cardiologist, taking into consideration the emerging safety data from palbociclib trials and the investigator's best medical judgment.
Grade 4	Discontinue palbociclib and remove from protocol therapy

1. QTc Prolongation

   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 and additional ECGs performed until QTc normalizes.

If such reversible causes are identified, then they should be corrected accordingly (ie, correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation (if possible) of concomitant medications known to prolong the QT interval).

8.4 Dose Modifications – Docetaxel (Closed to accrual per Revision #3)

DRUG	DOSE LEVEL*	DOSE
Docetaxel	Full	75 mg/m^2
	-1 Level	55 mg/m^2
	-2 Level	35 mg/m^2

* Only two docetaxel dose reductions are allowed.

Dose Modifications of Docetaxel

Hematological Toxicity	
Grade 4 Febrile Neutropenia	Hold docetaxel until recovery to ≤ Grade 1. Then resume docetaxel administration with one dose level reduction.
Grade 4 Neutropenia	Must undergo a dose reduction for subsequent cycles regardless of the duration of the neutropenia with a maximum of two dose reductions.
Grade 4 Thrombocytopenia	Hold docetaxel until recovery to ≤ Grade 1. Then resume docetaxel administration with one dose level reduction.
Hepatic Toxicity	
Grade ≥ 3	Hold docetaxel up to two weeks. If recovered to ≤ Grade 1, resume treatment at one level dose reduction. Otherwise, remove from protocol treatment.
Grade 2	Reduce docetaxel at a one level dose reduction.
Non-Hematological Toxicity	
Grade 4 Vomiting	If occurs despite antiemetic prophylaxis, restart treatment after recovery to ≤ Grade 1 at a one level dose reduction.
Grade ≥ 3 Diarrhea	If occurs despite antidiarrheal treatment, restart treatment after recovery to ≤ Grade 1 at a one level dose reduction.
Grade 2 Peripheral Neuropathy	One dose level reduction.
Grade 3 Peripheral Neuropathy	Remove from protocol treatment.
Grade 3 Fluid Retention	Hold docetaxel until recovery to ≤ Grade 1, then restart treatment at a one level dose reduction.
Grade ≥ 3 Stomatitis	Hold docetaxel until recovery to ≤ Grade 1, then restart treatment at a one level dose reduction.
For All Other Non-Hematological Toxicities	**Actions**
Grade ≥ 3	Hold docetaxel until recovery to ≤ Grade 1, then restart treatment at a one level dose reduction.

a. Hypersensitivity Reactions

No dose reductions will be made for any hypersensitivity reactions.
If, despite dexamethasone pre-treatment, the patient experiences a hypersensitivity reaction, treatment should be as indicated in the following table.

Grade 1:	• Consider decreasing the rate of infusion until recovery to < Grade 1. • Then, resume infusion at the initial planned rate.

Grade 2:	• Stop docetaxel infusion and give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV. • Resume docetaxel infusion after recovery < Grade 1; depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate (e.g., infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, then finally, resume at the hour infusion rate). • Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, (e.g., infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, and finally, administer at the 1-hour infusion rate).
Grade ≥ 3	• REMOVE FROM PROTOCOL TREATMENT

In case of late occurring hypersensitivity symptoms, e.g., appearance within 1 week of treatment of a localized or generalized pruritis, symptomatic treatment may be given (e.g., oral antihistamine). Additional oral or IV premedication with antihistamine may also be given for the next cycle of treatment depending on the intensity of the reaction observed.

b. Fluid Retention

If symptomatic, patients developing fluid retention may be treated with diuretics at the treating investigator's discretion. Spironolactone at a starting dose of 25 mg TID plus furosemide 20-40 mg PRN is recommended.

c. Hepatic Dysfunction

Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Dose Modifications for Abnormal Liver Function

Bilirubin	Alkaline Phosphatase	AST or ALT	Action
> IULN or	> 2.5 x IULN or	> 1.5 x IULN	Wait ≤ 2 weeks. If recovered*, retreatment should be at one level dose reduction. If not, remove from protocol treatment.

* Bilirubin ≤ IULN AND alkaline phosphatase ≤ 2.5 x IULN, AND AST or ALT ≤ 1.5 x IULN.

Note: A maximum of two dose reductions per patient are allowed.
IULN = institutional upper limit of normal.

d. Stomatitis

If stomatitis is present on Day 1 of any cycle, treatment should be withheld until the stomatitis has resolved.

e. Other Non-hematological Toxicities

Manage toxicities ≤ Grade 2 symptomatically, if possible, and retreat without dose reduction.

If toxicities ≥ Grade 3, drug should be held until resolution to ≤ Grade 1, then reinstituted, if medically appropriate, with a one level dose reduction.

Unacceptable toxicity from docetaxel is defined as one or more of the following:

Grade ≥ 3 nonhematologic toxicity (excluding nausea and vomiting) despite 2 prior dose reductions

Severe fluid retention not responsive to symptomatic therapy or dose reduction

Grade 4 vomiting despite antiemetics and dose reductions

Grade 4 hematologic toxicity despite two prior dose reductions. However, Grade 4 neutropenia must be either > 7 days in duration or must be accompanied by fever (single elevation in oral temperature > 38.5°C) requiring parenteral antibiotics or with documented infection to be considered an unacceptable toxicity (despite two prior dose reductions).

8.5 Dose Modification Contacts

For treatment or dose modification questions, please contact Drs. Martin J. Edelman and Kathy S. Albain at S1400CMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the **S1400C** must be reported to the Operations Office, Study Coordinator and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Arm 1 Palbociclib

REQUIRED STUDIES	PRE-STUDY	Cycle 1				Cycle 2				Cycle 3				Cycle 4				Subsequent Cycles	At Off Tx	Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
		WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7	WK 8	WK 9	WK 10	WK 11	WK 12	WK 13	WK 14	WK 15	WK 16	β			
PHYSICAL																					
History & Physical Exam	X					X		X		X				X				X	X	X	
Weight & Performance Status	X					X		X		X				X				X	X	X	
Disease Assessment Ω	X							X Ω						XΩ				XΩ		XΩ	
Toxicity Notation						X		X		X				X				X	X	x ɗb	X ɗb
Smoking Status Assessment	X																		X		
LABORATORY																					
CBC/Diff/Platelets/Hgb	X	X€				X		X		X				X				X	X	x ɗb	x ɗb
Serum Bilirubin	X	X€				X		X		X				X				X	X	x ɗb	x ɗb
ALT or AST	X	X€				X		X		X				X				X	X	x ɗb	x ɗb
Serum Creatinine/Calc CrCl	X	X€				X		X		X				X				X	X	x ɗb	x ɗb
Na, K, Cl, Ca, Mg	X	X€				X		X		X				X				X	X	x ɗb	x ɗb
HbA1c †	X									X								X		x ɗb	x ɗb
LDH ¥	X																				
Albumin ¥	X																				
X-RAYS AND SCANS																					
CT or MRI for Disease Assessment Ω	X							X Ω						XΩ				XΩ		XΩ	
Brain CT/MRI	X																				
EKG ◇	X							X													
Image Submission Σ	X							X						X				X		X	

Calendar 9.1 continues on next page. Click here for footnotes.

REQUIRED STUDIES	PRE-STUDY	Cycle 1				Cycle 2				Cycle 3				Cycle 4				Subsequent Cycles	At Off Tx	Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
		WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7	WK 8	WK 9	WK 10	WK 11	WK 12	WK 13	WK 14	WK 15	WK 16				
SPECIMEN SUBMISSION																					
Tissue for Banking																					X§
Blood for Banking #	X					X		X		X											Xð
TREATMENT																					
Arm 1: (28 day cycle)																					
Palbociclib		X	X	X		X	X	X		X	X	X		X	X	X		X			

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.
NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/QA/Documents/Best%20Practices%20upddate.pdf.

Footnotes for Calendar 9.1 (Palbociclib):

Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.2 of **S1400C**) must be repeated every 6 weeks (± 7 day window) until disease progression.

Σ Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400C**.

β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle, unless otherwise noted. Disease assessments and image submission are to take place every 6 weeks (± 7 days window).
Treatment and evaluation will continue until any of the criteria in Section 7.4 is met.

Δ After off treatment prior to progression, patients should be followed by repeating indicated laboratory tests every 3 months or more often as clinically indicated for the first year, then every 6 months for up to 3 years from date of sub-study registration. Disease assessment should continue every 6 weeks until progression.

√ After off treatment and after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at the end of year 3 from date of sub-study registration. Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study.

§ With patient's consent, an additional research biopsy within 1 month after the time of first progression among patients who had a response to palbociclib (in the opinion of the treating physician) must be collected. See Section 15.0 of **S1400C**

◇ EKG must be performed in triplicate to calculate QTc interval.

† HbA1c is required on Day 1 of every third cycle and at off treatment prior to progression.

With patients consent additional research blood draws will be collected (see Section 15.0 of **S1400C**).

¥ Results of these tests do not determine eligibility but are recommended prior to sub-study registration.

€ If the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated.

ɒ Assessments should continue until resolution of all acute adverse events.

ð Blood for Banking specimen must be collected at first progression after study treatment (see Section 15.0 of **S1400C**).

9.2 Arm 2 Docetaxel

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β				
REQUIRED STUDIES	PRE-STUDY	WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7	WK 8	WK 9	WK 10	WK 11	WK 12	WK 13	WK 14	WK 15	Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
PHYSICAL																		
History & Physical Exam	X				X			X			X			X			X	
Weight & Performance Status	X				X			X			X			X			X	
Disease Assessment Ω	X							X						X			X	
Toxicity Notation					X			X			X			X			X	
Smoking Status Assessment	X																X	
LABORATORY																		
CBC/Diff/Platelets/Hgb	X				X			X			X			X			X	
Serum Bilirubin	X				X			X			X			X			X	
ALT or AST	X				X			X			X			X			X	
Alkaline Phosphatase	X				X			X			X			X			X	
Serum Creatinine/Calc CrCl	X				X			X			X			X			X	
HbA1c π	X							X						X			X	
Na, K, Cl, Ca, Mg	X				X			X			X			X			X	
LDH ¥	X																	
Albumin ¥	X																	
X-RAYS AND SCANS																		
CT or MRI for Disease Assessment Ω	X							X						X			X	
Brain CT/MRI	X																	
EKG ◇	X							X										
Image SubmissionΣ	X							X						X			X	
SPECIMEN SUBMISSION																		
Blood for Banking *ƒ*	X				X			X			X							X

Calendar 9.2 continues on next page. Click here for footnotes.

REQUIRED STUDIES	PRE-STUDY	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β			Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15		
TREATMENT																		
Arm 2: (21 day cycle)																		
Docetaxel		X			X			X			X			X				
Dexamethasone		X			X			X			X			X				

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes for Calendar 9.2 (Docetaxel):

Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.2 of **S1400C**) must be repeated every 6 weeks (± 7 day window) while on treatment until disease progression.
Σ Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400C**.
β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle. Disease assessments are to take place every 6 weeks. Assessments will follow Best Practices for SWOG Studies: http://swog.org/Visitors/QA/Documents/Best%20Practices%20upddate.pdf, however the disease assessment window is ± 7 days. Treatment and evaluation will continue until criteria in Section 7.4 are met.
Δ After off treatment prior to progression, patients should be followed by repeating indicated tests every 3 months for the first year, then every 6 months for up to 3 years from date of sub-study registration.
√ After off treatment and after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of year 3 from date of **S1400C** registration.
f With patient's consent, an additional research blood draw must be collected (see Section 15.0 of **S1400C)**.
π HbA1c is required on Day 1 of every third cycle and at off treatment prior to progression.
¥ Results of these tests do not determine eligibility but are recommended prior to sub-study registration.
◇ EKG must be performed in triplicate to calculate QTc interval.

9.3 Arm 3 Re-Registration Palbociclib

REQUIRED STUDIES	Step 2 Re-Registration	Cycle 1				Cycle 2				Cycle 3				Cycle 4				Subsequent Cycles	At Off Tx	Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
		WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7	WK 8	WK 9	WK 10	WK 11	WK 12	WK 13	WK 14	WK 15	WK 16	β			
PHYSICAL																					
History & Physical Exam	X					X		X		X				X				X	X	X	
Weight & Performance Status	X					X		X		X				X				X	X	X	
Disease Assessment Ω	X							X Ω						XΩ				XΩ		XΩ	
Toxicity Notation						X		X		X				X				X	X	Xdb	Xdb
Smoking Status Assessment	X																		X		
LABORATORY																					
CBC/Diff/Platelets/Hgb	X	X€				X		X		X				X				X	X	Xdb	Xdb
Serum Bilirubin	X	X€				X		X		X				X				X	X	Xdb	Xdb
ALT or AST	X	X€				X		X		X				X				X	X	Xdb	Xdb
Serum Creatinine/Calc CrCl	X	X€				X		X		X				X				X	X	Xdb	Xdb
Na, K, Cl, Ca, Mg	X	X€				X		X		X				X				X	X	Xdb	Xdb
HbA1c †	X									X								X		Xdb	Xdb
LDH ¥	X																				
Albumin ¥	X																				
X-RAYS AND SCANS																					
CT or MRI for Disease Assessment Ω	X							X Ω						XΩ				XΩ		XΩ	
Brain CT/MRI	X																				
EKG ◇	X							X													

Calendar 9.3 continues on next page. Click here for footnotes.

REQUIRED STUDIES	Step 2 Re-Registration	Cycle 1				Cycle 2				Cycle 3				Cycle 4				Subsequent Cycles	At Off Tx	Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
		WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7	WK 8	WK 9	WK 10	WK 11	WK 12	WK 13	WK 14	WK 15	WK 16	β			
SPECIMEN SUBMISSION																					
Tissue for Banking																					X§
Blood for Banking #	X					X		X		X											XÐ
TREATMENT																					
Arm 3: (28 day cycle)																					
Palbociclib		X	X	X		X	X	X		X	X	X		X	X	X		X			

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.
NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/QA/Documents/Best%20Practices%20updddate.pdf.

Footnotes for Calendar 9.3 (Re-Registration Palbociclib):

Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.2 of **S1400**) must be repeated every 6 weeks (± 7 day window) until disease progression.

Σ Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400C**.

β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle, unless otherwise noted. Disease assessments and image submission are to take place every 6 weeks. (± 7 days window).
Treatment and evaluation will continue until any of the criteria in Section 7.4 is met.

Δ After off treatment prior to progression, patients should be followed by repeating indicated laboratory tests every 3 months or more often as clinically indicated for the first year, then every 6 months for up to 3 years from date of sub-study registration. Disease assessment should continue every 6 weeks until progression.

√ After off treatment and after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at the end of year 3 from date of re-registration. Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study.

§ With patient's consent, an additional research biopsy within 1 month after the time of first progression among patients who had a response to palbociclib (in the opinion of the treating physician) must be collected. See Section 15.0 of **S1400C**

◇ EKG must be performed in triplicate to calculate QTc interval.

† HbA1c is required on Day 1 of every third cycle and at off treatment prior to progression.

With patients consent additional research blood draws will be collected (see Section 15.0 of **S1400C**).

¥ Results of these tests do not determine eligibility but are recommended prior to re-registration

€ If the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated.

ȸ Assessments should continue until resolution of all acute adverse events.

ð Blood for Banking specimen must be collected at first progression after study treatment (see Section 15.0 of **S1400C**).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

See Section 10.0 of **S1400** for criteria for evaluation and endpoint analysis.

11.0 STATISTICAL CONSIDERATIONS

This study will employ Design #2: the Seamless Phase II followed by Phase III design as described in **S1400** Section 11.2a. A complete description of the statistical design and analysis plan is included in Section 11.0 of **S1400**. This section includes details specific to **S1400C**

11.1 Primary Objective and Biomarker Prevalence

The primary objective within **S1400C** is to evaluate palbociclib among patients defined to be cell cycle gene alteration positive. Cell cycle gene alteration positive is defined as the presence of any of the eligible alterations in the following table:

Gene	Alteration type	Eligible alteration
CDK4	Substitution	None
	Fusion	None
	Amplification	FMI standard thresholds: ≥ 6 estimated copies (or ≥ 7 in triploid, ≥ 8 in tetraploid+ samples)
CCND1	Substitution	None
	Fusion	None
	Amplification	FMI standard thresholds: ≥ 6 estimated copies (or ≥ 7 in triploid, ≥ 8 in tetraploid+ samples)
CCND2	Substitution	None
	Fusion	None
	Amplification	FMI standard thresholds: ≥ 6 estimated copies (or ≥ 7 in triploid, ≥ 8 in tetraploid+ samples)
CCND3	Substitution	None
	Fusion	None
	Amplification	FMI standard thresholds: ≥ 6 estimated copies (or ≥ 7 in triploid, ≥ 8 in tetraploid+ samples)

The expected prevalence of cell cycle gene alteration is 13.9% and the expected frequency of the other sub-study biomarkers among cell cycle gene alteration positive patients is: 2.8% for FGFR, 1.9% for PI3K, and 2.8% for MET. Based on simulation using the randomization ratios as defined in **S1400** Section 11.1, the expected frequency of patients assigned to **S1400C** is 11.7%.

11.2 Sample Size and Accrual

Phase II Design: **S1400C** will follow the Phase II design from the Seamless Phase II followed by Phase III (see Section 11.2c of **S1400**) among patients defined to be Cell cycle gene alteration positive. Assuming that 5% of patients will be ineligible, the total accrual

goal to the Phase II study is 42 patients. The anticipated duration of accrual to the phase II is 26-30 months from study activation.

12.0 DISCIPLINE REVIEW

This section does not apply to this sub-study.

13.0 REGISTRATION GUIDELINES

See Section 13.0 of **S1400** for registration guidelines.

13.1 Registration Timing

Patients must plan to begin treatment within 7 working days after Step 1: sub-study registration and Step 2: re-registration.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3 for details.

14.3 Data Submission Procedures

a. All participating institutions must submit data electronically via the Web using Medidata Rave® at the following url: https://login.imedidata.com/selectlogin.

1. If prompted, select the 'CTEP-IAM IdP' link.

2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed.
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table on Page 5 of **S1400**.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF SUB-STUDY REGISTRATION, SUBMIT:

S1400C Onstudy Form

Smoking Status Assessment Form

Baseline Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at baseline (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease at baseline as specified in Section 15.3.

b. WITHIN 7 DAYS AFTER STEP 2 RE-REGISTRATION:

Submit the following:

S1400C Re-Registration Eligibility Verification Form

Baseline Tumor Assessment Form (RECIST 1.1)

Smoking Status Assessment Form

Radiology reports from all scans performed to assess disease at baseline (NOTE: Upload reports via the Source Documentation Baseline form found in the Re-Registration folder form in Rave)

c. IF PATIENT CONSENTS, SUBMIT SPECIMENS:

Specimens as specified in Section 15.0 of **S1400C**

d. IMMEDIATELY AFTER EACH CYCLE (Arm 1, Palbociclib [and Arm 3 Re-Registration]): 1 Cycle = 28 days; Arm 2, Docetaxel: 1 Cycle = 21 OF TREATMENT, SUBMIT:

S1400C Treatment Form

S1400C Adverse Event Form

S1400C Laboratory Values Form

For Cycle 1 only: submit the **S1400C** Pre-Treatment Laboratory Values Form

e. WITHIN 14 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION (see **S1400C** Section 9.0 for Disease Assessment Schedule), SUBMIT:

Follow-Up Tumor Assessment Form (RECIST 1.1) documenting results of assessment

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in Section 15.3.

f. WITHIN 7 DAYS OF DISCONTINUATION OF TREATMENT, (INCLUDING BOTH ON INITIAL TREATMENT ARM AND RE-REGISTRATION TREATMENT), SUBMIT

Off Treatment Notice documenting reasons for off treatment

Smoking Status Assessment Form

S1400C Treatment Form

S1400C Adverse Event Form

S1400C Laboratory Values Form

g. ONCE OFF TREATMENT SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1400C** REGISTRATION*, THEN AT THE END OF YEAR 3 FROM SUB-STUDY/RE-REGISTRATION* SUBMIT:

Advanced NSCLC Follow-Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

*For patients registered to Step 2 (Re-Registration), the follow-up schedule is calculated from the date of Step 2 re-registration registration.

Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study (see Section 14.4j).

h. WITHIN 7 DAYS OF PROGRESSION/RELAPSE (BOTH ON INITIAL TREATMENT ARM AND RE-REGISTRATION TREATMENT ARM), SUBMIT:

Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in Section 15.3.

i. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information. In addition, if the patient was still on protocol treatment, submit materials specified in **S1400C** Section 14.4 or if patient was no longer on treatment, submit a final Advanced NSCLC Follow-Up Form.

j. Data Submission FOR PATIENTS WHO HAVE PROGRESSED AND WISH TO REGISTER TO A NEW SUB-STUDY:

WITHIN 7 DAYS OF PROGRESSION/RELAPSE:

Submit the **S1400** Request for New Sub-Study Assignment Form under **S1400** in Rave® Continue follow-up on **S1400C** per Sections 9.0 and 14.4 until registration to a new sub-study. See Section 14.6 of **S1400** for additional data submission requirements following request for new sub-study assignment.

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

See **S1400** Section 5.1 for SWOG Specimen Tracking System (STS) instructions.

15.2 Correlative Studies and Banking (Optional for Patients)

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) are considered optional for the patient:

a. With patient's consent, specimens must be collected and submitted as follows:

1. Peripheral Blood:

Specimens must be collected at the following times during both Step 1 and Step 2 (Re-Registration).

Arm 1- Palbociclib:
- Pre-study (see Section 15.3 of **S1400**)
  Note: If a patient provided blood at pre-screening at the time of progression on current treatment or screening (see Section 15.3 of **S1400**) and registration to **S1400** was within 42 days from sub-study registration, then that blood specimen can count as pre-study blood
- Weeks 5, 7, 9- - Patients that go off treatment are not required to continue to submit specimens.

First Progression after study treatment

Arm 2- Docetaxel:
- Screening/Pre-screening (see Section 15.3 of **S1400**)
- Weeks 4, 7, 10
- First progression after study treatment.

Arm 3- Palbociclib:
- Pre-study (see Section 15.3 of **S1400**)

Note: If a patient provided blood at pre-screening at the time of progression on current treatment or screening (see Section 15.3 of **S1400**) and registration to **S1400** was within 42 days from sub-

study registration, then that blood specimen can count as pre-study blood
- Weeks 5, 7, 9 - Patients that go off treatment are not required to continue to submit specimens.
- First Progression after study treatment

Approximately 8-10 mL of blood must be collected in EDTA tubes. Blood should be processed within one hour after venipuncture. If immediate processing within this time frame is not possible, EDTA tubes that are not processed immediately should be refrigerated at 4˚C. The approximate time from collection to processing should be recorded as part of the patient's source documentation. EDTA tubes must be centrifuged at 800 g for 10 minutes at 4˚C for the collection of plasma. Plasma must be transferred to one 15 ml centrifuge tube and spun again at 800 g for an additional 10 minutes. Plasma must then be pipetted into 1 ml coded cryovials at 0.5 ml aliquots. Plasma must be clear before freezing; no cells or debris should be present. Each buffy coat layer (the gray-white layer at the interface of blood cells and plasma, approximately 1 ml) from the blood tube must each be transferred into appropriately labeled 2-ml cryovials. Samples must be placed immediately in a -80˚C freezer to ensure long-term viability.

2. New Biopsy of Tumor at Time of Progression Among Responders to Palbociclib:

A new biopsy is strongly requested from patients who responded to protocol treatment (in the opinion of the treating physician) and then experienced disease progression. Biopsies will be used for molecular analysis of molecular characteristics associated with mechanisms of resistance. New biopsy should be either bronchoscopy/surgical biopsy or CT guided biopsy. The biopsy should be performed within one month after progression as FFPE material. The minimum requirement as a block or 12 unstained sections.

b. Specimen Submission

Samples for multiple patients can be shipped in batches, at least every 3 months if not more frequently, to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201.

Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp).

c. Specimen collection kits are not being provided for this submission; sites must use institutional supplies.

15.3 Radiology Review (Required)

CT, PET/CT, and/or MRI images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for central data collection and quality control (QC) check as well as retrospective central review.

a. CT, PET/CT, and/or MRI images must be submitted to IROC Ohio for central review at the following timepoints for both Step 1 and Step 2 (Re-Registration):

- Baseline
- Every 6 weeks until progression

All study participants must have a CT (or MR or PET/CT) exam prior to sub-study entry. Participants must then undergo additional imaging every 6 weeks until progression of disease. The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (see Section 10.1c). Each exam should be performed per Section 18.1c. IROC will perform a QC of the imaging exams.

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinical appropriate considerations.

Central review of scans will not be triggered if the study will not be submitted to the FDA for the investigational therapy. Central review of scans will be triggered only if deemed necessary for FDA evaluation. A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions, can be found in Section 18.1c.

b. TRIAD Digital Image Submission

TRIAD is the secure electronic image upload application utilized for IROC Services of this trial. TRIAD de-identifies and validates the images as they are transferred.

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Ohio. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account (see Section 13.2).

- To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

2. TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

Questions regarding image submissions, including TRIAD, should be directed to SWOG1400@irocohio.org or call IROC Ohio at 614-293-2929.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse event reporting use the NCI's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1 or 16.2, as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in Arm 1 and Arm 3 of this study is palbociclib. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Palbociclib, Arm 1 or Re-Registration, Arm 3:

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events (if applicable) are found in Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1) **Group-specific instructions.**

Supporting Documentation Submission - Within 5 **calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

a. Printed copy of the first page of the CTEP-AERS report
b. Copies of clinical source documentation of the event
c. If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent used in Arm 2 of this study is docetaxel. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on study Arm 2 who have received the commercial drug(s) listed in Section 16.1 above within 30 days of the last administration of the commercial agent(s).

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AER**

CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event[b].

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention,

radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known,

accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

   *Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

   NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

   The Pregnancy Information Form is available at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

17.0 BIBLIOGRAPHY

1 Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. J Clin Oncol 24:1770-83, 2006.

2 Arnold A, Papanikolaou A. Cyclin D1 in breast cancer pathogenesis. J Clin Oncol 23:4215-24, 2005.

3 Buckley MF, Sweeney KJ, Hamilton JA, Sini RL, Manning DL, Nicholson RI, et al. Expression and amplification of cyclin genes in human breast cancer. Oncogene 8:2127-33, 1993.

4 Gillett C, Fantl V, Smith R, Fisher C, Bartek J, Dickson C, et al. Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining. Cancer Res 54:1812-7, 1994.

5 Roy PG, Thompson AM. Cyclin D1 and breast cancer. Breast 15:718-27, 2006.

6 Rudas M, Lehnert M, Huynh A, Jakesz R, Singer C, Lax S, et al. Cyclin D1 expression in breast cancer patients receiving adjuvant tamoxifen-based therapy. Clin Cancer Res 14:1767-74, 2008.

7 Finn RS, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res 11:R77, 2009.

8 Network CGAR. Comprehensive genomic characterization of squamous cell lung cancers. Nature 489:519-25, 2012.

9 Network CGAR. Comprehensive genomic characterization of squamous cell lung cancers. Nature 489:519-25, 2012.

10 Bandla S, Pennathur A, Luketich JD, Beer DG, Lin L, Bass AJ, et al. Comparative genomics of esophageal adenocarcinoma and squamous cell carcinoma. Ann Thorac Surg 93:1101-6, 2012.