June 21, 2018

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #14 to EAY131-Z1B, *Molecular Analysis for Therapy Choice (MATCH): MATCH Treatment Subprotocol Z1B: Phase II Study of Palbociclib (PD-0332991) in Patients with Tumors with CCND1, 2, 3 Amplification.*

This addendum is in response to Dr. Fernanda Arnaldez's June 7, 2018 Request for Rapid Amendment for Palbociclib.

The following revisions to the EAY131-Z1B protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	3.3	Updated the Palbociclib CAEPR list with Version 2.3, January 25, 2018.

The following revisions to the EAY131-Z1B Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date.
2.	What possible risks can I expect from taking part in this study?	Updated the possible risks language and the Palbociclib condensed risk list with Version 2.3, January 25, 2018.

If you have any questions regarding this addendum, please contact ali@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to EAY131-Z1B so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

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ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAY131-Z1B

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol Z1B: Phase II Study of Palbociclib (PD-0332991) in Patients with Tumors with CCND1, 2, 3 Amplification

PALBOCICLIB TREATMENT SUBPROTOCOL CHAIR: Amy S. Clark, MD
PALBOCICLIB TREATMENT SUBPROTOCOL CO-CHAIR: Richard Finn, MD
PALBOCICLIB TRANSLATIONAL CHAIR: Angela DeMichele, MD, MSCE

Version Date: June 21, 2018

NOTE: This subprotocol (EAY131-Z1B) should be used in conjunction with the MATCH Master Protocol (EAY131).

Rev. Add13 **NOTE: As of 11/17, all protocol changes will be noted by addendum number. Please reference the activation memo for the addendum activation date.**

SUBPROTOCOL ACTIVATION DATE

May 31, 2016 (Incorporated in Addendum #3)
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #13
Addendum #14

Agent	IND#	NSC#	Supply
Palbociclib	IND Sponsor: DCTD, NCI IND#:		NCI Supplied

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Table of Contents

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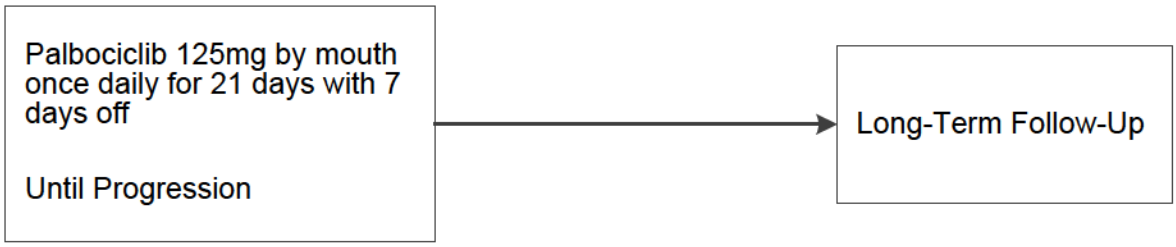
Rev. 3/17

Schema



Cycle = 28 days
Accrual Goal: 70

1. Introduction

1.1 Palbociclib

1.1.1 Background

Palbociclib is an oral inhibitor of CDK4 and CDK6 with potency in the nanomolar range [1]. In preclinical models, it causes G1 arrest in cells that express the retinoblastoma (Rb) protein.

Phase I studies of palbociclib examined two different dosing schedules, 2 weeks on with 1 week off (2/1) [2] and 3 weeks on with 1 week off (3/1) [3]. The MTD for the 2/1 schedule was 200mg and 125 for the 3/1 schedule. Both schedules were safe and notable prolonged stable disease was observed in patients receiving palbociclib in both treatment schedules. In total, over 1000 patients have received palbociclib in Phase I-III trials. There are currently 5 ongoing studies using palbociclib as a monotherapy in various solid and liquid malignancies and over 15 using it in combination with other agents (chemotherapy, endocrine therapy and targeted therapy) to treat a variety of malignancies as well as early stage breast cancer.

Based on randomized Phase II data, palbociclib (brand name Ibrance) received accelerated approval from the FDA in combination with letrozole on February 3, 2015 for treatment of metastatic ER+ breast cancer in the first line metastatic setting and was approved in combination with fulvestrant based on randomized Phase III data on March 2, 2016. Thus, additional hundreds of patients are currently receiving palbociclib now as part of standard therapy for metastatic ER+ breast cancer. There are currently 16 completed, 42 ongoing and 12 planned clinical trials examining palbociclib as of March 18, 2016.

1.1.2 Pharmacokinetics

In plasma collected from patients enrolled on the Phase I trials, palbociclib concentrations were detectable 1 hour following oral administration. This indicates rapid absorption. Pharmacokinetics did not vary among the schedules or within each trial, and PK did not appear to be dose dependent over a dose-range from 25 to 225 mg flat dosing. The volume of distribution of palbociclib is around 3000 L, which is high and indicates substantial tissue binding. The half life of palbociclib is 26h and demonstrates the appropriateness of once daily dosing. Extended PK analyses are not available; however the reproducible toxicity of the drug over long-term dosing indicates that drug accumulation is unlikely. Excretion has not been characterized in detail, however is predominantly non-renal given a measured renal excretion of less than 2% [2, 3].

1.1.3 Toxicity

Palbociclib has a consistent side effect profile across a multitude of studies. Neutropenia is the most common grade 3 or 4 adverse event, occurring in approximately 50-62% of patients receiving the drug. Febrile neutropenia is extremely infrequent, occurring in 0-3% of patients [4-7]. The most common adverse events attributable to

palbociclib among patients in the randomized Phase II and Phase III trials including palbociclib are fatigue (40%), thrombocytopenia (16%-22%), anemia (29%-35%), nausea (25%-29%), diarrhea (19%-21%), and alopecia (15%-20%). Thromboembolic events were also reported in 2-5% of patients who received palbociclib on these trials [5, 6].

1.1.4 Efficacy

The efficacy of single agent palbociclib is variable across tumor types. In a Phase I study examining the 3 on 1 off schedule, patients with RB+ liposarcoma, renal cell, germ cell tumor, breast cancer, thymoma, appendiceal and ovarian cancer all achieved stable disease for at least 4 months. In the phase I study examining the 2 weeks on 1 off schedule, one patient with RB+ testicular cancer had a partial response. A pharmacodynamic study of palbociclib in patients with RB+ mantle cell lymphoma harboring the translocation t(11;14), resulting in increased cyclin D1 activity, demonstrated a 65% disease control rate.[8] Another phase II study in patients with CDK4-amplified liposarcoma revealed a 66% progression free survival at 12 weeks.[4] In a heavily pretreated metastatic breast cancer population, the clinical benefit rate was 19% [7] The addition of palbociclib to letrozole in the first line metastatic setting doubled the progression free survival (PFS) from 10.2 months in the letrozole alone arm to over 20 months in the combination [5]. It was with this data that palbociclib received accelerated approval from the FDA. Moreover, when combined with fulvestrant, another anti-hormone therapy used to treat metastatic ER+ breast cancer that had progressed on one line of endocrine therapy and/or chemotherapy, the addition of palbociclib improves the PFS from 3.8 months with fulvestrant alone to 9.2 months with the combination [6]. Thus, palbociclib can be used for the treatment of ER+ metastatic breast cancer in the first line and beyond. Its utility in triple negative breast cancer is not established nor is its effectiveness in combination with endocrine therapy from heavily pretreated patients with ER+ metastatic breast cancer.

1.2 Supporting Preliminary Data

1.2.1 CCND1 Amplification

CCND1 amplification has been reported in 30% of primary breast cancers [9]. However, it is also observed in other tumors. In an ongoing phase 2 trial at the University of Pennsylvania (Penn) of palbociclib in *CCND1* amplified RB+ tumors (amplification defined as CCND1: CEP17 > 2.0) the stable disease and PR rate was as high as 41% for some tumors (Table 1). In the randomized Phase 2 PALOMA1 study [5], evaluating letrozole with or without palbociclib in ER+ breast cancer, patients whose tumor additionally had CCND1 amplification had a significant benefit from the addition of palbociclib. This finding confirmed the preclinical data supporting the importance of estrogen signaling in ER-positive tumors [10]. However, the role of CCND1 amplification and response to CDK 4/6 inhibition outside of this population has not been thoroughly studied, and thus is the question being addressed in this study.

Table 1: Frequencies of CCND1 Amplification in Penn Study and TCGA

Tumor Type	Number Screened	Number with *CCDN1* Amplification from Penn Study (% positive)	Number with SD ≥ 6mo or PR/Number Enrolled (%)	Number with *CCND1* Amplification from TCGA (% positive)
Breast	143	26 (18.2 %)	5/16 (31%)	79 (16.4%)
Colon	41	1 (2.4%)	0/1 (0%)	n/a
Esophageal	20	8 (40%)	0/4 (0%)	51 (55.4%)
Gastric	20	2 (10%)	0/1 (0%)	18 (6.3%)
SCC (Head & Neck)	5	2 (40%)	0/1 (0%)	77 (27.6%)
Osteosarcoma	1	1 (100%)	NA/0	n/a
Renal Cell	1	1 (100%)	NE/1	1 (0.6%)

NA: Not available

NE: Not evaluable

1.2.2 Rationale for Palbociclib in CCND1 Amplified tumors

The cell cycle is frequently altered in malignancies. These alterations include mutations in cyclin/cdk components, gene amplification of regions of the genome that encode them, or overexpression of individual proteins that relate to cell cycle proteins, the consequence of these alterations leads to a cell's adoption of a hyperproliferative program. Specifically, the components of the first step in the G1-S Checkpoint- the CDK 4/6-Cyclin D complex are each altered with different frequencies across a variety of solid malignancies. Amplification in *CCND1* is reported (as described above) and results in overabundance of the cyclin D proteins and thus a higher number of activated CDK4/6-Cyclin D complexes with the ultimate consequence of more cells entering proliferation. Inhibition of this complex by a specific inhibitor, such as palbociclib, should stop this higher rate of proliferation by arresting cells in G1.

Because CDK4 and CDK 6 also bind to Cyclin D2 and 3, it is plausible that amplifications of their genes (CCND2 and CCND3) could also increase the number of activated CDK4/6-Cyclin D complexes in a cell and increase cellular proliferation. There is much less data on the frequency with which CCND2 or 3 are amplified or altered in human cancers. Examination of the TCGA database has demonstrated that CCND2 is amplified (specific definition not provided) in 20.8% of 149 germ cell tumors, 11.3% of 311 ovarian cancer tumors, 6.2% of 178 cases of squamous cell carcinoma of the lung, 6.4% of 109 pancreatic cancer cases, 5.4% of uterine carcinosarcoma cases, 6.7% of 283 low grade gliomas, and 1-5% of glioblastomas, breast cancers, sarcoma, and esophageal cancers. CCND3 is amplified in 6.4% of 109 cases of pancreatic cancers, 7.6% of 184 cases of esophageal carcinoma, 6.3% of uveal melanomas, 4.9% of 287 cases of diffuse large B cell lymphomas, stomach adenocarcinoma, and in 1-5% of cutaneous melanomas, sarcomas, non-small cell lung cancer (squamous cell and adenocarcinoma), urothelial carcinoma, hepatocellular carcinoma, endometroid carcinoma, ovarian carcinoma, invasive bladder cancer, adrenocortical carcinoma, colorectal adenocarcinoma, prostate cancer, squamous cell carcinoma of the head and neck, mesothelioma, and papillary renal cell cancer.

Given the importance of the RB gene product in mediating response to CDK 4/6 inhibition, it is hypothesized that Rb loss would be associated with resistance to palbociclib regardless of CCND1 copy number changes [10]. For this reason, the presence of RB expression will be confirmed in all tumors prior to enrollment.

2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the MATCH Master Protocol, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: All patients must have signed the relevant treatment consent form

2.1 Registration to Treatment

_____ 2.1.1 Patients must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master Protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

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_____ 2.1.2 Patients must have amplification of CCND1, 2, or 3, or another aberration, as determined via the MATCH Master Protocol and according to Appendix II. See Appendix II for information on the targeted mutations and corresponding Levels of Evidence.

_____ 2.1.3 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block).

Date of ECG: _____

_____ 2.1.4 Patients must not have known hypersensitivity to Palbociclib or compounds of similar chemical or biologic composition.

_____ 2.1.5 Patients must not have breast cancer, mantle cell lymphoma or myeloma.

_____ 2.1.6 Patients with known or symptoms of left ventricular dysfunction will be excluded.

_____ 2.1.7 Patients must not have had prior treatment with Palbociclib, Ribociclib, Abemaciclib or any other CDK4/6 inhibitors.

_____ 2.1.8 Patients must not be using drugs or foods that are known potent CYP3A4 inhibitors or inducers, or are CYP3A substrates with narrow therapeutic indices (See Appendix III of this subprotocol).

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3. Palbociclib Treatment Plan

3.1 Administration Schedule

3.1.1 Palbociclib 125 mg, by mouth with food once daily for 21 days with 7 days off.

Repeat 28 day cycles until progression.

3.2 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 subprotocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

3.2.1 Additional instructions, requirements and exceptions for protocol EAY131 – Subprotocol Z1B

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

EAY131 – Subprotocol Z1B specific expedited reporting requirements:

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on palbociclib, or within 28 days of the subject's last dose of palbociclib, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master Protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131 – Subprotocol Z1B specific expedited reporting exceptions:

For Subprotocol Z1B, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

3.2.2 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

3.2.3 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Palbociclib (PD-0332991, NSC 772256)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). 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 1751 patients*. Below is the CAEPR for Palbociclib (PD-0332991).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Version 2.3, January 25, 2018[1]

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 5.0 Term) [n= 1751]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
		Febrile neutropenia	
EYE DISORDERS			
	Blurred vision		
	Dry eye		
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INFECTIONS AND INFESTATIONS			
Infection[10]			***Infection[10] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 5.0 Term) [n= 1751]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache[11]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Epistaxis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		
	Skin and subcutaneous tissue disorders - Other (rash)[12]		

[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 fulvestrant.

[4]Rash includes rash, rash maculo-papular, erythema, erythematous rash, erysipelas, rash pruritic, rash papular, generalized rash, exanthema, allergic dermatitis, dermatitis acneiform, and dermatitis.

[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; Blood and lymphatic system disorders - Other (pancytopenia)

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Cardiac disorders - Other (paroxysmal atrial fibrillation with rapid ventricular response); Palpitations; Pericarditis; Sinus bradycardia; Supraventricular tachycardia

EYE DISORDERS - Cataract; Eye disorders - Other (retinal hemorrhage)

GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Colitis; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Esophageal stenosis; Flatulence; Gastric hemorrhage; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Intra-abdominal hemorrhage; Lower gastrointestinal hemorrhage; Small intestinal obstruction; Small intestinal perforation; Upper gastrointestinal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema limbs; Localized edema; Malaise; Non-cardiac chest pain; Pain; Sudden death NOS

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 - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Creatinine increased; Ejection fraction decreased; GGT increased; INR increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; 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; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (osteomyelitis); Myalgia; Neck pain; Osteonecrosis; 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)[13]; Syncope

PSYCHIATRIC DISORDERS - Confusion; Insomnia; Psychiatric disorders - Other (altered mental status)

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Oropharyngeal pain; 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.

3.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Dose Level	Palbociclib Dose
1	125 mg PO QD
-1	100 mg PO QD
-2	75 mg PO QD

Discontinuation of palbociclib for more than 2 weeks (excluding rest days) will result in the removal of the patient from the study.

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Table 2: Hematologic Toxicities: Dose Modification and Management for Day 1 of all Cycles and Day 14 of Cycles 1 and 2

CTCAE Grade	Dose Modification
Grade 1 or 2	No dose adjustment is required.
Grade 3	Day 1 of all Cycles: Withhold palbociclib, repeat complete blood count monitoring in 1 week. When recovered to Grade ≤ 2, start the next cycle at the same dose Day 14 of Cycles 1 and 2: Continue palbociclib at current dose to complete cycle. Repeat complete blood count on Day 21. Consider dose reduction in cases of prolonged (> 1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles
Grade 3 + Fever ≥ 38.5 and/or infection	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤ 2. Resume at next lower dose.
Grade 4	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤ 2. Resume at next lower dose.

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Table 3: Non-hematologic Toxicities: Dose Modification and Management for Day 1 of all Cycles

CTCAE Grade	Dose Modification
Grade 1 or 2	No dose adjustment is required.
Grade ≥ 3 non-hematologic toxicity (if persisting despite medical treatment)	Withhold until adverse event resolves to: • Grade ≤ 1 • Grade ≤ 2 (if not considered a safety risk for the patient) Resume at next lower dose

3.5 Supportive Care

3.5.1 All supportive measures consistent with optimal patient care will be given throughout the study, with the exception of growth factor support, which can be provided at the investigator's discretion per ASCO guidelines.

3.6 Duration of Agent-specific treatment

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression

3.7 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

4. Study Parameters

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4.1 Therapeutic Parameters for Palbociclib Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving Palbociclib treatment.

NOTE: All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation and electrocardiogram (ECG).

Test/Assessment	Prior to Registration to Treatment	Treatment			End of Treatment	Follow Up[F]
		Every Cycle, prior to treatment	Cycle 1 & 2, Day 14	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X	X[J]				X
Performance status	X	X[J]				X
CBC w/diff, plts[B]	X	X[J]	X[L]			X
Serum chemistry[B]	X	X[J]				X
Radiologic evaluation[D]	X			X[D]		X[F]
β-HCG[C]	X					
Toxicity Assessment[G]		X			X	X[F]
Pill Count/Diary[H]		X			X	
ECG[K]	X	X[I]				
Rev. 3/17 Tumor biopsy and blood sample for MATCH Master Protocol[E]				X	X	

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

C. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment.

D. Disease measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional

information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

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E. Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

F. Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

G. Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person. The Toxicity Assessment is not required prior to Cycle 1, but is required every subsequent cycle.

H. The pill calendar will be collected at the end of every cycle. The Pill Count/Diary is not required prior to Cycle 1, but is required every subsequent cycle.

I. As clinically indicated.

J. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this timepoint: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications.

K. Within 8 weeks of treatment assignment.

L. Mid-cycle blood tests are only required for Cycle 1 and Cycle 2.

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5. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment subprotocol prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by eligible participating Investigators (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 – see general information) The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). 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.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an "active" account status, a "current" password, and an active person registration status.

NCI Supplied Agent(s) – General 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 or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: 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).

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Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator.

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Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

5.1 Palbociclib (PD-0332991) (NSC 772256)

5.1.1 Other Names:

PD 0332991-00 (free base), PD 0332991-0054 (isethionate salt), Ibrance

5.1.2 Classification:

Cyclin-dependent kinase (CDK) inhibitor

5.1.3 Mode of Action:

Palbociclib is a highly selective and reversible oral inhibitor of cyclin-dependent kinases 4 and 6. Inhibition of Cdk 4/6 results in cell cycle arrest from G1 to S phase.

5.1.4 Storage and Stability:

Storage: Store at 20-25°C (68-77°F); excursions permitted between 15-30° C (59-86° F).

Stability: Refer to the package label for expiration.

5.1.5 Dose Specifics:

Palbociclib 125 mg, by mouth once daily for 21 days with 7 days off.

5.1.6 Preparation:

Palbociclib capsules are supplied by Pfizer, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as commercially labeled 21-count bottles in the following strengths:

- 75 mg hard gelatin capsule (size 2) with light orange cap and body, printed with white ink “Pfizer” on the cap and “PBC 75” on the body.
- 100 mg hard gelatin capsule (size 1) with caramel cap and light orange body, printed with white ink “Pfizer” on the cap and “PBC 100” on the body.
- 125 mg hard gelatin capsule (size 0) with caramel cap and body, printed with white ink “Pfizer” on the cap and “PBC 125” on the body.

Capsule excipients include microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate. Gelatin capsule colorants include red iron oxide, yellow iron oxide, and titanium dioxide. White printing ink contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone.

5.1.7 Route of Administration:

Oral. Take by mouth once daily with a meal.

5.1.8 Incompatibilities:

In vitro data suggest that palbociclib is primarily metabolized by CYP 3A4. Avoid any concomitant CYP 3A4 strong inhibitors or inducers during palbociclib administration. *In vivo* studies demonstrate that palbociclib is a weak inhibitor of CYP3A4; thus any sensitive

substrates of CYP 3A4 should be used with caution on study especially substrates with a narrow therapeutic index.

Palbociclib is a weak inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) drug efflux transporters. The potential for interaction is considered low at clinically-relevant doses of palbociclib.

5.1.9 Side Effects:

See Section 3.3 for side effects.

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5.1.10 Nursing/Patient Implications

Women of child bearing potential (WOCBP) and men should use effective methods of contraception from the time of signing the informed consent though 16 weeks after the last dose of study agent, or agree to completely abstain from heterosexual intercourse. Also, women should not breastfeed until at least 3 weeks after completing treatment with the study agent.

6. Translational Studies

Please refer to the MATCH Master Protocol for information on the Translational Studies.

7. References

1. Fry DW, Harvey PJ, Keller PR et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Molecular cancer therapeutics 2004; 3: 1427-1438.
2. Schwartz GK, LoRusso PM, Dickson MA et al. Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (Schedule 2/1). British journal of cancer 2011; 104: 1862-1868.
3. Flaherty KT, Lorusso PM, Demichele A et al. Phase I, dose-escalation trial of the oral cyclin-dependent kinase 4/6 inhibitor PD 0332991, administered using a 21-day schedule in patients with advanced cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 2012; 18: 568-576.
4. Dickson MA TW, Keohan ML, D'Angelo SP, Gounder MM, Chi P et al. Phase II Trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified liposarcoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013; 31.
5. Finn RS, Crown JP, Lang I et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. The Lancet. Oncology 2015; 16: 25-35.
6. Turner NC, Ro J, Andre F et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. The New England journal of medicine 2015; 373: 209-219.
7. DeMichele A, Clark AS, Tan KS et al. CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. Clinical cancer research : an official journal of the American Association for Cancer Research 2015; 21: 995-1001.
8. Leonard JP, LaCasce AS, Smith MR et al. Selective CDK4/6 inhibition with tumor responses by PD0332991 in patients with mantle cell lymphoma. Blood 2012; 119: 4597-4607.
9. Roy PG, Pratt N, Purdie CA et al. High CCND1 amplification identifies a group of poor prognosis women with estrogen receptor positive breast cancer. International journal of cancer. Journal international du cancer 2010; 127: 355-360.
10. Finn RS, Dering J, Conklin D 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. 2009;11(5):R77.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1B: Palbociclib/CCND1, 2, 3

Appendix I

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Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each capsule.
2. Take the capsules with food once daily for 21 days, and then take no study medicine for 7 days (rest days). Each cycle is 28 days long.
3. Palbociclib capsules must be swallowed whole.
4. If you forget, the missed capsules will not be taken later.
5. If you vomit after taking your scheduled dose, it will not be made up or re-taken. You will continue to receive the next scheduled doses as prescribed.
6. Please bring the empty bottle or any leftover capsules and your pill calendar to your next clinic visit.
7. Store palbociclib capsules at room temperature.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused capsules and your completed pill calendar to your doctor's visits.

Palbociclib

DAY	Date			Time capsules taken	Number of capsules taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year			
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
Days 22-28 are rest days – Do not take any capsules.						

Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1B: Palbociclib/CCND1, 2, 3

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Appendix II

Actionable Mutations for Sub-Protocol EAY131-Z1B

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description	Rb IHC[1]
CCND1	CCND1	CNV	2	Amplification	Positive
CCND2	CCND2	CNV	2	Amplification	Positive
CCND3	CCND3	CNV	2	Amplification	Positive

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1. Rb IHC will be done on archived specimens; those patients that are + on IHC for archived tumor specimens will be counted in the primary analysis. It is estimated, based on MATCH screening results to date, that at least 90% of patients will have Rb expression in their tumor.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1B: Palbociclib/CCND1, 2, 3

Appendix III

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Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **Palbociclib.** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Palbociclib is a major (sensitive) substrate of the liver enzyme CYP3A4

- **Palbociclib** is a time dependent inhibitor of CYP3A4
- Drug interactions with medications that are strong inhibitors or potent inducers of CYP3A4 may occur
- Drug interactions with medications that are major substrates of CYP3A4 with a narrow therapeutic range may occur

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

There is some risk that **Palbociclib** will interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Palbociclib must be used very carefully with other medicines that need certain liver enzymes to be cleared from the body. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors or substrates of CYP 3A4 (a liver enzyme)."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit juice and grapefruit while taking Palbociclib.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is

_____

and he or she can be contacted at:

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **Palbociclib.** This clinical trial is sponsored by the NCI. **Palbociclib** may interact with other drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement
- **Palbociclib** interacts with a specific liver enzyme called **CYP3A4**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors or substrates of CYP3A4"**

Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.

Your study doctor's name is

_____ and can be

contacted at _____

1. Fry DW, Harvey PJ, Keller PR et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Molecular cancer therapeutics 2004; 3: 1427-1438.
2. Schwartz GK, LoRusso PM, Dickson MA et al. Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (Schedule 2/1). British journal of cancer 2011; 104: 1862-1868.
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7. DeMichele A, Clark AS, Tan KS et al. CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. Clinical cancer research : an official journal of the American Association for Cancer Research 2015; 21: 995-1001.
8. Leonard JP, LaCasce AS, Smith MR et al. Selective CDK4/6 inhibition with tumor responses by PD0332991 in patients with mantle cell lymphoma. Blood 2012; 119: 4597-4607.

9. Roy PG, Pratt N, Purdie CA et al. High CCND1 amplification identifies a group of poor prognosis women with estrogen receptor positive breast cancer. International journal of cancer. Journal international du cancer 2010; 127: 355-360.
10. Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC. In.
11. Headache has been observed in trials using Palbociclib (PD-0332991) in combination with fulvestrant. In.
12. Rash includes rash, rash maculo-papular, erythema, erythematous rash, erysipelas, rash pruritic, rash papular, generalized rash, exanthema, allergic dermatitis, dermatitis acneiform, and dermatitis. In.
13. Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC. In.