August 19, 2020

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 #25 to EAY131-Z1C, *MATCH Treatment Subprotocol Z1C: Phase II Study of Palbociclib (PD-0332991) in Patients with Tumors with CDK4 or CDK6 Amplification.*

This addendum is in response to a Request for Rapid Amendment for Palbociclib from Dr. Charles Kunos dated November 19, 2019, and also, Dr. Tali Johnson's Amendment Request for updates to specific protocol language for Palbociclib dated June 5, 2020.

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

This addendum has been reviewed and approved by the Central IRB, which is the sole IRB of record for this study. Local IRB review and approval is unnecessary.

Implementation of this addendum must occur on the activation date. Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

Re: Review of Amendment #36 of Protocol #EAY131-Z1C: "MATCH Treatment Subprotocol Z1C: Phase II Study of Palbociclib (PD-0332991) in Patients with Tumors with CDK4 or CDK6 Amplification." The following are ECOG-ACRIN's responses to the CTEP review comments dated 5/26/2020. Please note that the Principal Investigator's comments appear in bold below.

I. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
1.	**ICD – "**Why is this study being done?**"**	Under **Why is this study being done?** on page 1, please change the target accrual back to 49, consistent with protocol amendment #35: There will be about ~~35~~ 49 people taking part in this study. **PI Response: Thank you. This has been corrected to reflect the approved accrual expansion to 49 patients.**

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

II. Recommendations:

#	Section	Comments
2.	3.2.1	The Summary of Changes state that, "In second box, under "Pregnancies" revised language referencing "subject" to "female patient," however this change does not appear to have been made. Please revise the section below accordingly. **EAY131 – Subprotocol Z1C 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. **PI Response: Thank you. This has been corrected.**

III. Company Comments – Requiring a Response:

#	Section	Comments
3.	3.4	We noticed that pneumonitis was added as ADR but in the section of the dose modification guidelines and Grade 4 event, the language would allow for treatment to be resumed at the lower dose, which does not align with our recommendations to permanently discontinue palbociclib with severe ILD or pneumonitis. **PI Response: Thank you. We've revised the language to discontinue pablociclib for Grade 4 non-hematologic toxicity for pneumonitis or ILD.**

II. Additional Protocol Changes by Principal Investigator:

The following revisions to the EAY131-Z1C protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date and addendum number.
2.	3.2.1	In second box, under "Pregnancies" revised language referencing "subject" to "female patient".
3.	3.3	Updated the Palbociclib CAEPR to Version 2.4 September 13, 2019.
4.	Appendix III	Updated patient drug information template format.

The following revisions to the EAY131-Z1C Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date.
2.	Possible Side Effects Palbociclib	Updated the condensed risk list for Palbociclib to Version 2.4, September 13, 2019.

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

We request review and approval of this addendum to EAY131-Z1C so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol Z1C: Phase II Study of Palbociclib (PD-0332991) in Patients with Tumors with CDK4 or CDK6 Amplification

PALBOCICLIB TREATMENT SUBPROTOCOL CHAIR: Mark O'Hara, MD
PALBOCICLIB TREATMENT SUBPROTOCOL CO-CHAIR: Mark Dickson, MD
PALBOCICLIB TRANSLATIONAL CHAIR: Angela DeMichele, MD, MSCE

Version Date: August 19, 2020

NOTE: This subprotocol (EAY131-Z1C) should be used in conjunction with the MATCH Master Protocol (EAY131).

SUBPROTOCOL ACTIVATION DATE

March 13, 2017 (Incorporated in Addendum #7)
Addendum #13
Addendum #14
Addendum #24
Addendum #25

Agent	IND#	NSC#	Supply
Palbociclib	IND Sponsor: DCTD, NCI IND#:	772256	NCI Supplied

Table of Contents

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Schema

Cycle = 28 days
Accrual Goal: 49

1. Introduction

1.1 Palbociclib

1.1.1 Background

Cell cycle dysregulation is a hallmark of most common malignancies, including mutations in cyclin/cyclin-dependent kinase (cdk) components, gene amplification of regions of the genome that encode cyclins and cdks, overexpression of individual proteins that relate to cell cycle proteins, or inactivation of the key proteins that serve as regulated inhibitors of the cell cycle. As a consequence of these alterations, cells adopt a proliferative program. In the G1 to S transition, cyclin D proteins associate with Cdk4 or Cdk6 to form an activating complex that catalyzes phosphorylation of the tumor suppressor retinoblastoma protein (Rb), which in turn allows for the subsequent activation of the E2F-dependent transcription.

Palbociclib is a highly selective, reversible oral inhibitor of CDK 4 and 6. Preclinical studies show that palbociclib reversibly arrests cancer cells in G1, preventing progression to S phase, through reduction of Rb phosphorylation at CDK4/6-specific sites. This inhibition results in accumulation of Rb positive tumor cells in G1, down regulation of genes regulated by E2F, reduction of Ki-67, and tumor regression (1).

Two phase 1 studies evaluating differing dosing schedules of palbociclib were completed. The first phase 1 study tested increasing doses of palbociclib on a two week on, one week off schedule (2/1) and determined that the maximum tolerated dose was 200mg daily (2). The second study evaluated a three week on, one week off schedule (3/1) and determined the 125mg daily dose to be the recommended phase 2 dose (3). Both phase 1 studies show that palbociclib is well tolerated with the main toxicity of myelosuppression. The 125mg dose given on 3/1 schedule is the dosing schedule that was moved into phase II and III studies of palbociclib given a reliable safety profile and efficacy, and therefore is the dose used in this study.

1.1.2 Pharmacokinetics

In plasma collected from patients enrolled on the Phase I trials above, palbociclib concentrations were detectable 1 hour following oral administration, but was slowly absorbed with a median time of maximum concentration of 4-7 hours and slowly eliminated with a median elimination half-life of 26-26.7 hours (2, 3). This demonstrates appropriateness of the daily dosing schedule. Furthermore, the geometric mean volume of distribution was significantly greater than total body water, indicating extensive distribution to peripheral tissues (2, 3). Extended PK analyses are not available; however the reproducible toxicity of the drug over long-term dosing indicates that drug accumulation is unlikely. Metabolism is the major route of elimination of palbociclib, with excretion in stool and urine playing a minimal role.

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 events, occurring in approximately 35-54% of patients receiving single agent palbociclib, though only 2.7-3.3% of patients experienced febrile neutropenia (4-6). Other grade 3 or 4 hematologic toxicities occur less frequently, including thrombocytopenia in 19-30% and anemia in 5-13%. Non-hematologic toxicities include fatigue (10-14%), nausea (5-12%), and diarrhea (3.3-6%) (4-6).

1.1.4 Efficacy

Palbociclib has been evaluated both as a single agent and in combination with hormone therapy in breast cancer. In the Phase I study noted above examining single agent palbociclib on the 3/1 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 (3). In the phase I study examining 2/1 schedule, one patient with RB+ testicular cancer had a partial response (2). 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 (6). 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% (5). 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 (7). 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 patients with metastatic ER+ breast cancer who 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 (8). Thus, palbociclib can be used for the treatment of ER+ metastatic breast cancer in the first line and beyond.

1.2 Supporting Preliminary Data

1.2.1 CDK 4 and CDK6 amplification

Aberrations of Cdk4, Cdk6, and cyclin D, all found with varying frequencies across malignancies, are associated with increased cellular proliferation. More specifically, as demonstrated in the TCGA and other databases, amplification of *CDK4* or *CDK6* is noted in a variety of cancers and has been correlated with overexpression and increased cellular proliferation in cancer tissues (see Table 1) (9-14).

Table 1

Tumor Type	Cases of amplified CDK6 (%)	Cases of amplified CDK4 (%)
Esophageal carcinoma	13%	
Gastric adenocarcinoma	7.3%	4%
Head and neck squamous cell carcinoma	7.2%	<1%
Pancreatic adenocarcinoma	5.5%	3-6%
Lung squamous cell carcinoma	5.6%	
Bladder urothelial carcinoma	3.9%	2%
Prostate adenocarcinoma	3.6%	5%
Lung adenocarcinoma	3.5%	7%
Glioblastoma multiforme	3.3%	16-18.5%
Hepatocellular carcinoma	2.6%	
Sarcoma	3%	18-24%

CDK4 and CDK6 frequencies from cBIOPortal (13)

1.2.2 Rationale for Palbociclib in CDK4 and CDK6 amplified tumors

1.2.2.1 Preclinical Studies

Though *CDK4* or CDK6 amplification is relatively common and has oncogenic properties (15), studies targeting *CDK4* or *CDK6* amplification are limited. Preclinical studies of CDK4/6 inhibition have shown specific inhibition of both Cdk6 and Cdk6- and Cdk4-induced Rb phosphorylation, leading to decreased cell cycle proliferation (16, 17). Furthermore, Barton KL et al demonstrate sensitivity to PD-0332991 (palbociclib) in a brainstem glioma mouse model with CDK4 amplification (18). Moreover, in Zhang YX et al, CDK4-amplified liposarcoma demonstrated significant sensitivity to LEE011, another CDK4/6/ inhibitor, in cell lines and in mouse xenograft assays (14). CDK6 was overexpressed in rhabdomyosarcoma cell lines that were sensitive to LEE011 (19), and CDK4 and CDK6 amplified pancreatic neuroendocrine xenografts (20) and glioblastoma cell lines with CDK6 amplification were sensitive to inhibition by palbociclib (21).

1.2.2.2 Clinical Studies

Palbociclib has been evaluated in phase II studies in CDK4 amplified liposarcoma. While the response rates in published reports of palbociclib are relatively low at 3% as a single agent in this population progression free survival is enhanced, demonstrating a 66% 3 month progression free survival rate (4), with median progression free survival ranging from 18-24 weeks depending on dosing schedule (22) and 35-40% 6 month progression free survival rate on the 3 week on, 1 week off schedule (pending publication).

To the best of our knowledge, there are no clinical studies in patients with *CDK6* amplified tumors with a *CDK4/6* inhibitor. However, as noted above in the preclinical studies, palbociclib has shown beneficial effect in this pathway.

Rev. Add24

1.3 Arm Expansion

1.3.1 In some circumstances, it may necessary to expand a treatment arm if an inadequate number of assays from Designated Laboratories can be confirmed by the central Oncomine® Assay to ensure 31 evaluable patients for the primary endpoint. In those circumstances, the study will be expanded to achieve a total of 35 patients, i.e. the number of cases to allow for attrition so that at least 31 patients are evaluable for the primary endpoint. An additional 14 patients will be accrued in this expansion, i.e. expanded from 35 to 49. If planned accrual is not completed within 21 months, the expansion cohort will be closed to further accrual.

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).

Rev. Add13

_____ 2.1.2 Patients must have CDK4 amplification or CDK6 amplification, 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 breast cancer, mantle cell lymphoma, myeloma, or liposarcoma.

_____ 2.1.5 Patients must not have known hypersensitivity to palbociclib or compounds of similar chemical or biologic composition.

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

_____ 2.1.7 Patients must not have received prior therapy with a CDK4 or CDK6 inhibitor (including but not limited to palbociclib, abemaciclib, or ribociclib).

_____ 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 on days 1-21 of the 28 days cycle (3 weeks on, 1 week 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 Z1C

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.

Rev. Add25

EAY131 – Subprotocol Z1C 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 female patient is on palbociclib, or within 28 days of the female patient'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 Z1C specific expedited reporting exceptions:

For Subprotocol Z1C, 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.

Rev. Add14

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 2.4, September 13, 2019[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[2]			***Infection[2] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***

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%)**	
	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[3]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Epistaxis		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		
	Skin and subcutaneous tissue disorders - Other (rash)[4]		

[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)[5]; 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; 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.

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 e.g. pneumonitis, ILD should cause discontinuation of palbociclib)

CTCAE Grade	Dose Modification
	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

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]				
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.

Rev. Add13 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 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 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).

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.

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.

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

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Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1C: Palbociclib/CDK4, 6

Appendix I

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each capsule.
2. The capsules should be taken 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 Z1C: Palbociclib/CDK4, 6

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Appendix II

Actionable Mutations for Sub-Protocol EAY131-Z1C

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description	Rb IHC[1]
CDK4	CDK4	CNV	2	Amplification	Positive
CDK6	CDK6	CNV	2	Amplification	Positive

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 Z1C: Palbociclib/CDK4, 6

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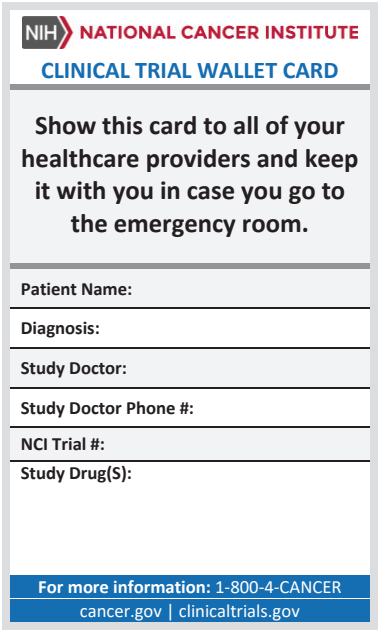
Appendix III

PATIENT CLINICAL TRIAL WALLET CARD


NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov