A Phase II Single Arm Study of Palbociclib in Patients with Metastatic HER2-positive Breast Cancer with Brain Metastasis

Principal Investigator: Massimo Cristofanilli, MD
Professor of Medicine
Associate Director of Translational Research and Precision Medicine
Department of Medicine-Hematology and Oncology
Robert H Lurie Comprehensive Cancer Center
Feinberg School of Medicine
710 N Fairbanks Court, Olson Building, Suite 8-250A
Chicago, IL 60611
Tel: 312-503-5488
Email: Massimo.cristofanilli@nm.org

NU Sub-Investigator(s): *Northwestern University*
Robert H. Lurie Comprehensive Cancer Center

Priya Kumthekar, MD
Jonathan Strauss
Luis Blanco
Sofia Garcia

Northwestern Lake Forest Hospital
Valerie Nelson, MD

Affiliate Site PIs: Jenny Chang, MD
Houston Methodist Hospital/Houston Methodist Cancer Center
6445 Main Street, P24-326
Houston, Texas 77030
Tel: 713-441-9948
jcchang@houstonmethodist.org

Biostatistician: Alfred Rademaker
rademaker@northwestern.edu

Study Intervention(s): Palbociclib (Ibrance)

IND Number: *Exempt*

IND Holder: N/A

Funding Source: *Pfizer*

Version Date: **August 15, 2017 (Amendment 5)**

Coordinating Center: **Clinical Research Office**
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
676 N. St. Clair, Suite 1200
Chicago, IL 60611
http://cancer.northwestern.edu/CRO/index.cfm

Table of Contents

STUDY SCHEMA 5

STUDY SUMMARY 6

1.0 Introduction – BACKGROUND & RATIONALE 7

2.0 OBJECTIVES & endpoints 11

3.0 PATIENT ELIGIBILITY 11

4.0 TREATMENT PLAN 14

5.0 STUDY PROCEDURES 18

6.0 ENDPOINT ASSESSMENT 22

7.0 ADVERSE EVENTS 23

8.0 DRUG INFORMATION 27

9.0 CORRELATIVES/SPECIAL STUDIES 30

10.0 STATISTICAL CONSIDERATIONS 32

11.0 STUDY MANAGEMENT 33

REFERENCES 37

APPENDICES 39

APPENDIX 1 39

APPENDIX 2 39

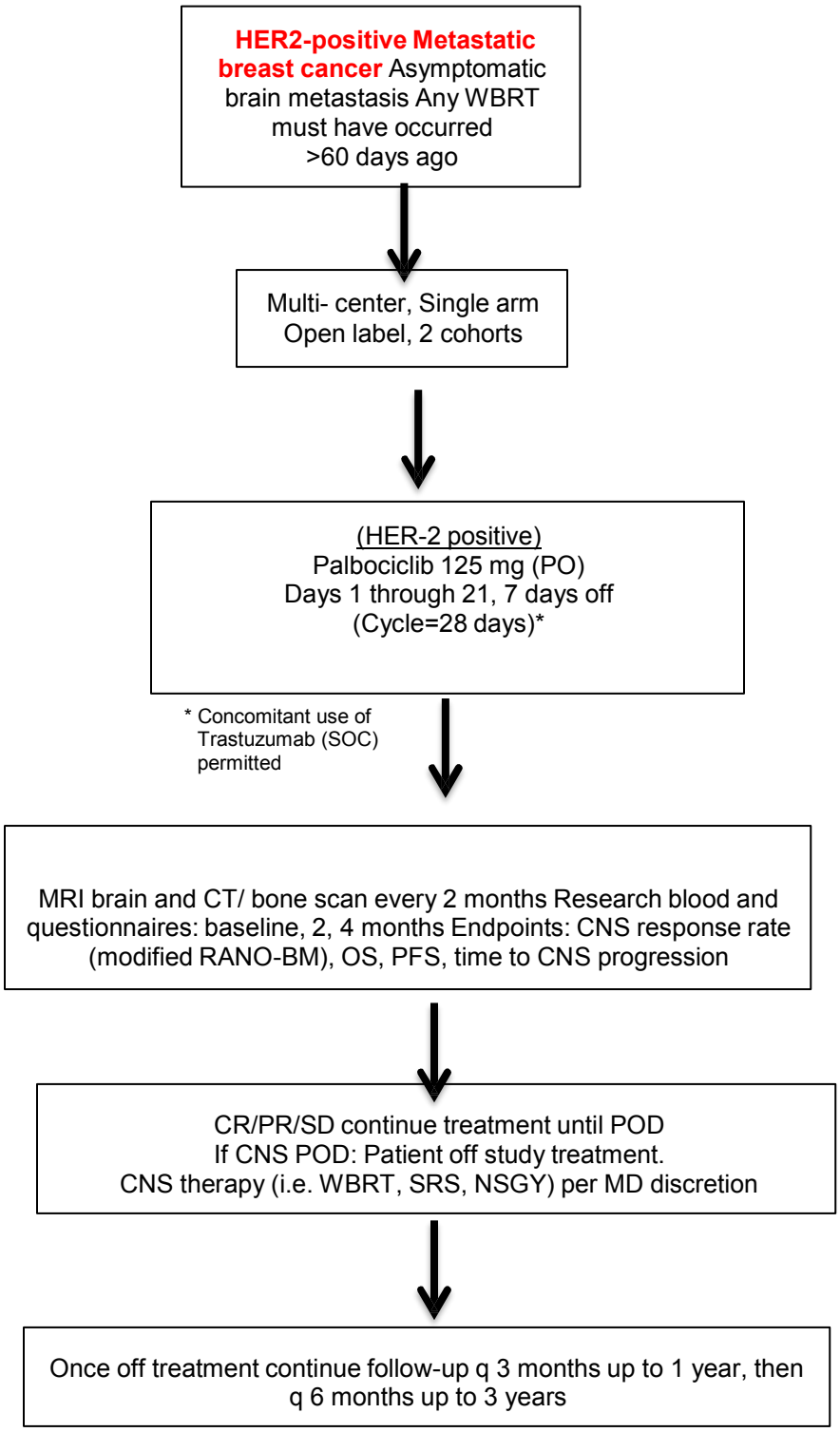
APPENDIX 3 40

History of Amendment summary of changes 41

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&PE	History & Physical Exam
HER-2	Human epidermal growth factor receptor 2
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSGY	Neurosurgery
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SV	Screening visit
SOC	Standard of Care
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
SRS	Stereotactic radiosurgery
WBC	White Blood Cells
WBRT	whole brain radiation therapy

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase II, multi-center, open label study of Palbociclib in patients with Metastatic HER2-positive Breast Cancer with Brain Metastasis
Short Title	Palbociclib in HER2-positive Breast Cancer Brain Metastasis
Version	August 15, 2017 (Amendment 5)
Study Design	A phase 2 study enrolling patients with metastatic HER2-positive breast cancer who have asymptomatic brain metastasis.. Patients will be treated with 125mg of PO palbociclib (21 days on, 7 days off). In addition, they can be enrolled and treated concurrently with Trastuzumab. MRI of the brain will monitor for disease progression. Upon progression (CNS or systemic) patients will off study treatment and will receive CNS directed therapy (such as WBRT, SRS, surgery) per treating physician discretion.
Study Center(s)	Lead Site: Northwestern University Robert H. Lurie Comprehensive Cancer Center Affiliate Sites: Houston Methodist Hospital
Objectives	**Primary Objective:** 1. To determine the overall radiographic response rate in the CNS. **Secondary Objectives:** 1. To determine PFS, OS 2. Time to CNS progression 3. Overall response rate systemically 4. Safety and tolerability
Sample Size	Maximum accrual limit: 25patients Evaluable patients : 20(Her2-positive)
Diagnosis & Key Eligibility Criteria	**Key Inclusion Criteria:** 1. Histologically confirmed metastatic HER2-positive breast cancer 2. Measurable brain metastasis (at least 1 lesion >=5mm) 3. No systemic therapy 2 weeks prior to initiating palbociclib 4. ECOG Performance status ≤ 2 5. Trastuzumab allowed Adequate bone marrow and organ function (ANC >=1000, platelets >=100 000, hemoglobin >=10, GPT/GOT/bilirubin <3xULN (or <5xULN if liver metastasis), creatinine <1.5xULN) **Key Exclusion Criteria:** 1. Any clinically significant neurologic symptoms attributed to CNS metastasis 2. Leptomeningeal disease 3. Significant medical illness per investigators discretion
Treatment Plan	Patients will be treated with 125mg of PO palbociclib (21 days on, 7 days off). They will continue therapy while there is no evidence of disease progression. Upon CNS disease progression, patient will be off study treatment and will be treated with CNS directed therapy (such as WBRT, SRS, surgery) per treating physician discretion. If systemic progression occurs, patients will come off study
Statistical Methodology	To detect a radiographic response rates increase from 23% to 40% in the HER2-positive cohort,. A Bayesian posterior probability will be calculated after the response status in 20 patients has been assessed. The goal is that there is at least an 80% probability that the response rate exceeds 40% in the HER-2 positive cohort Then the total number of evaluable patients to be accrued is 20.

Introduction – BACKGROUND & RATIONALE

1.1 Disease Background

1.1.1 *Breast cancer incidence and subtypes.*

Breast cancer is the most common non-dermatological malignancy in women with an estimated 232, 670 new diagnoses in 2014; and is the second leading cause of cancer death in women with an estimated 40, 000 women in the United States succumbing to the disease in 2014(1). Breast cancer is a heterogeneous disease comprised of several molecular subtypes, which are commonly extrapolated into clinical subtypes based on receptor status(2). The specific receptors which are assessed in standard clinical practice are the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2-neu (HER2) receptor.

1.1.2 *Breast cancer and brain metastasis.*

Of patients diagnosed with early stage disease, less than 3% will develop brain metastasis, however, this number increases to approximately 10-16% in patients with metastatic disease (3, 4). Different subtypes of breast cancer have different incidences of brain metastasis, with the highest being luminal B (12%), HER2-positive (12%), luminal-HER2 (8%), and TNBC (7%), and the least common is luminal A subtype (0.7%). Approach to treatment of brain metastasis is a multidisciplinary effort involving medical and radiation oncologists, and neurosurgeons; primary modalities of therapy include surgery, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), and systemic treatments which can penetrate the blood brain barrier.

In select patients with larger tumors in surgically accessible areas, surgical resection of brain metastasis can be considered. The addition of WBRT to surgery can improve CNS progression rates, but has not been shown to improve overall survival (5, 6). However, performing surgery with WBRT rather than WBRT alone, can improve CNS recurrence rates (20% from 52%) and survival (40 weeks versus 15 weeks) (7). In patient with few discrete lesions, SRS can provide local control rates from 65-94%, and this has become an increasingly popular modality to treat brain metastasis (8-10). The addition of SRS to WBRT does not improve survival in general (6.5 months versus 5.7 months).However, in patients with single brain metastasis or favorable prognosis median survival may be improved (6.5 versus 4.9 months, 11.6 versus 9.6 months, respectively) (11).

The majority of systemic therapies do not cross the blood brain barrier (BBB), and have limited efficacy against CNS metastasis. Certain drugs including high dose methotrexate and capecitabine are sometimes used as they can cross the BBB, but there are no drugs specifically indicated for brain metastasis. Many agents have been investigated for the treatment of brain metastasis, with overall response rates (ORR) ranging from 0-40% (average ORR response rates in the CNS for chemotherapy are 17%), and time to progression (TTP) or progression free survival (PFS) ranging from <2months to 4months (average TTP/PFS 2.5 months) (**Table 1**) (14). For patients with HER-2 positive breast cancer, lapatinib with various combinations of chemotherapy has been investigated since lapatinib is a small molecule inhibitor that can cross the BBB. While response rates and PFS are better with this targeted approach, response rates range from 0-67% (average approximately 22.7%), and TTP/PFS ranging from 2.4 – 5.5months (average approximately 3.9 months) (**Table 2**) (12). Key reasons for the wide variability in response rates and PFS has to do with previous treatment, where generally those

with less previous CNS-directed therapies tend to have high ORR and TTP/PFS on these therapies.

Table 1. Response rates and TTP/PFS to chemotherapy.

Regimen	Number of Patients (Number of Breast Cancer Patients)	Patient Population	CNS ORR in Breast Cancer Subset	TTP/PFS
Temozolomide	19 (5)	Pretreated with systemic therapy	0%	<2 months
Temozolomide	157 (51)	80% prior chemotherapy for MBC 24% prior WBRT	4%	~2 months
Capecitabine + temozolomide	24 (24)	33% prior WBRT	18%	3 months
Cisplatin + temozolomide	32 (15)	~50% prior WBRT	40%	2.9 months
Cisplatin + etoposide	107 (56)	No prior CNS RT allowed; 36% chemotherapy naive	38%	4 months
Sagopilone	15 (15)	Progression after CNS RT required	13%	1.4 months
Patupilone	36 (36)	Progression after CNS RT required	19%	2.8 months
Vinorelbine + temozolomide	38 (11)	Heavily pretreated patients	0%	1.9 months

Table 2. Response rates and TTP/PFS to lapatinib based therapy.

Regimen	Number of Patients	Patient Population	CNS ORR	TTP/PFS
Lapatinib	39	Heavily pretreated	2.6%	3.0 months
Lapatinib	237	Progression after CNS RT required	6%	2.4 months
Lapatinib + capecitabine	50	Progression after CNS RT and through lapatinib monotherapy required	20%	3.6 months
Lapatinib + capecitabine	138	Heavily pretreated	18%	NR
Lapatinib + capecitabine	34	Heavily pretreated	21%	5.1 months
Lapatinib + capecitabine	22	Heavily pretreated	32%	5.1 months
Lapatinib + capecitabine	13	Heavily pretreated	38%	NR
Lapatinib + capecitabine	45	No prior CNS radiotherapy allowed	67%	5.5 months
Lapatinib + topotecan	9	Heavily pretreated	0%	NR
Lapatinib + temozolomide	17	Heavily pretreated	NR	2.8 months

1.1.3 *Palbociclib in breast cancer*.

Palbociclib is an oral small molecule inhibitor of cyclin dependant kinases (CDK) 4 and 6, which affect the growth cycle (13). The PALOMA-1 study was a Phase II randomized study in patients with metastatic ER-positive breast cancer which demonstrated the addition of palbociclib to letrozole in the front line setting which increased median progression free survival (PFS) from 10.2 months to 20.2 months (hazard ration (HR) 0.488, 95% confidence interval (CI) 0.319 – 0.748, p=0.0004), earning it Food and Drug Administration (FDA) approval (14). The results of the PALOMA-3 study was a larger Phase III study, which demonstrated the addition of palbociclib to fulvestrant which improved median PFS from 3.8

months to 9.2 months (HR 0.42, 95% CI 0.32 – 0.56, p<0.001). These studies provide strong rationale for the use of palbociclib in ER-positive breast cancer.

While basal like cancers do not tend to display alterations in cyclin D1 or CDK4/6, the PALOMA-1 study did not find these genomic aberrations to predict response to therapy.

Till date, palbociclib has been studied in combination with other agents. In this study, palbociclib is being studied as monotherapy, as well as in combination with trastuzumab.

Palbociclib crosses the blood brain barrier:

Palbociclib has been investigated in brain tumors. In vivo experiments in glioblastoma multiformans (GBM) has shown that palbociclib can suppress growth of GBM in intracranial xenografts, and prevented tumor-related death of treated mice (15). In these experiments, the brains of treated mice were dissected, showing that palbociclib was not only present in intracranial tissues, but was 25-35x higher in tumor tissue than in normal tissue (15). Another similar study in diffuse intrinsic pontine glioma (DIPG) mice models found that palbociclib had activity in intracranial tumors, and prolonged survival (16). Yet another study in preclinical GBM models, CDK4/6 inhibitors, including palbociclib have been found to cross the BBB and have antitumor activity (18). Recent studies, however, have shown that certain BBB transports, P-glycoprotein and Breast Cancer Resistance Protein (BCRP/ABCG2), can inhibit CNS uptake of palbociclib, although more studies are needed (18). Results from ongoing clinical trials in brain tumors (NCT02255461, NCT02530320) are ongoing

1.1.5 Rationale for target patient population:

There exists no clinical trial investigating CDK4/6 inhibitors in HER2- positive breast cancer, but several preclinical and translational studies exist that provide rationale. (21). While basal like cancers do not tend to display alterations in cyclin D1 or CDK4/6, the PALOMA-1 study did not find these genomic aberrations to predict response to therapy (14). Furthermore, HER2-positive breast cancers, have been demonstrated to require cyclin D1 and CDK4 for tumor progression and maintenance (5, 7). Palbociclib has been found to have single agent activity in transgenic HER2-positive models by causing near complete cessation of tumor proliferation, leading to improved survival of mice (7). These data provide rationale for the investigation of palbociclib in HER2-positive breast cancers.

1.1.6 Safety of trastuzumab in combination with other agents

This study will allow patients with HER2-positive disease to be treated concurrently with trastuzumab since it is usual practice to combine anti-HER2 therapy with other anti-cancer drugs in HER2-positive disease. In the pivotal study by Slamon and colleagues, the addition of trastuzumab to chemotherapy did not increase the risk of serious adverse events, other than cardiomyopathy, which is a well-established toxicity of trastuzumab (1). In patients who have progressed on trastuzumab, the continuation of trastuzumab in combination with other chemotherapy is a common practice. In studies that support this approach, the addition of trastuzumab added no increased toxicity. In a phase II study randomizing 78 patients to capecitabine with or without trastuzumab incidence of grade 3/4 was the same between both arms, with the only difference being a slightly higher incidence of grade 1/2 anemia in the trastuzumab arm (p=0.02) (2). As expected with trastuzumab, there was an increased incidence of decrease in left ventricular ejection fraction (LVEF), only 1 case was greater than grade 2. Of note, this study did not have a phase 1 component or safety run-in. In clinical practice, trastuzumab is routinely administered with cytotoxic chemotherapy safely (NCCN v3.2015). Routine standard of care practice is to evaluate LVEF with echocardiograms or MUGA scans routinely on any patients receiving trastuzumab.

1.1.7 Rationale for dose selection

The PALOMA-1 study was a Phase II randomized study in patients with metastatic ER-positive breast cancer which demonstrated the addition of palbociclib to letrozole in the front line setting which increased median progression free survival (PFS) from 10.2 months to 20.2 months (hazard ration (HR) 0.488, 95% confidence interval (CI) 0.319 – 0.748, p=0.0004), earning it Food and Drug Administration (FDA) approval (14). The recommended FDA dose and schedule of palbociclib is 125 mg daily for 21 consecutive days followed by 7 days off treatment and its dose and schedule is being used in this study

1.1.8 Patient Reported Outcomes: Questionnaires

Standard of care therapy to CNS lesions has significant toxicity. Patients who undergo WBRT can experience fatigue and decline in cognitive function (2). Patients undergoing SRS can have seizures, neurological deficits, nausea, headaches, and cognitive decline (3-5). These effects can have a significant impact on quality of life, therefore, we wish to assess if treatment with palbociclib affects quality of life, and in particular cognitive function. To assess cognitive function we will use the Functional Assessment of Cancer Therapy-Cognitive Function version 3.0 (FACT_Cog, ver 3.0) and to assess quality of life we will use the Functional Assessment of Cancer Therapy-Brain version 4.0 (FACT-Br) (available as stand-alone documents) They are both validated questionnaires that have been used in previous studies (www.facit.org).

2.0 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective & Endpoint

To determine the radiographic response rate in the CNS in patients with HER2-positive breast cancer who have brain metastasis treated with palbociclib.

2.2 Secondary Objectives & Endpoints

1) To determine the PFS and OS in patients with HER2-positive breast cancer who have brain metastasis treated with palbociclib.

2) To determine time to CNS progression in patients with HER2-positive breast cancer who have brain metastasis treated with palbociclib.

3) To determine systemic ORR in patients with HER2-positive breast cancer who have brain metastasis treated with palbociclib.

4) To determine the safety and tolerability of palbociclib in patients with HER2-positive breast cancer.

2.3 Exploratory Objectives & Endpoints

1)To evaluate circulating tumor DNA at baseline, 2 month and 4 months; particularly to assess cyclin D1 aberrations, and if this is predictive of responses.

2) To evaluate genomic landscape of available CNS and non-CNS tumors, and describe any discordance.

3) To evaluate cognitive function and quality of life at baseline, 2 and 4 months in patients receiving palbociclib.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with metastatic HER2-positive breast cancer who have asymptomatic brain metastasis. This will be a multi-center trial. Northwestern University will serve as the lead site and coordinating center for this study. Participating sites will include Houston Methodist Hospital.

A total of 20 evaluable subjects will be accrued. Approximately 1-2 potentially eligible patients are seen per month, and it is anticipated that at least 1 per month will be accrued (once all sites are up and running). Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Massimo Cristofanilli, at (312) 695-0990, or to the local PI at each participating site.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Histologically confirmed HER2-positive metastatic breast cancer (HER-2 3+ by immunohistochemistry. If IHC score of 2, FISH ratio must be greater than 2.0. If FISH less than 2.0, HER2 copy number must be greater than 6. NOTE: Brain

lesions are not required to have pathologic confirmation. ER-positive patients are allowed.

3.1.2 Patients must have a life expectancy of at least 12 weeks at the time of registration

3.1.3 Patients must be age ≥ 18 years. Both females and males are eligible.

3.1.4 ECOG performance status≤ 2(Appendix 1)

3.1.5 Measurable disease in the brain, defined as at least 1 lesion measuring ≥ 5 mm on imaging at the time of registration

3.1.6 If patients are on corticosteroids, they must have been on a stable or decreasing dose ≥ 5 days prior to obtaining their baseline Gd-MRI of brain. This MRI is to be obtained within 28 days of registration. NOTE: If patient needs escalation of steroids prior to therapy, or are on unstable doses of steroids they are not eligible.

3.1.7 Patients who underwent neurosurgery (NSGY, whole brain radiation therapy, or stereotactic radiosurgery (SRS) to a brain lesion must have a new measureable lesion. Previously surgically excised lesion/tumor bed, may be used as a measurable lesion if disease has progressed since surgery (NOTE: SRS may be done to a lesion that will not be used for response evaluation and should be done > 2 weeks prior to registration. Any WBRT must have occurred>60 days ago. Any NSGY procedure must have been completed >3 weeks prior to registration and baseline imaging).

3.1.8 Patients must not have received systemic therapy within 2 weeks of initiating palbociclib. NOTE: Patients on trastuzumab can remain on the drug if previously taking, or may start if not. No break or washout period required. Patients with ER-positive disease may not concurrently take endocrine therapy, however, no washout is required if they were previously on endocrine therapy. However, lapatinib, ado-trastuzumab-emtansine, and pertuzumab are prohibited and a minimum wash out period of 2 weeks is required.

3.1.9 Patients must exhibit adequate bone marrow, liver, and renal function, within 14 days prior to registration, defined as:

- ANC ≥ 1,000/mm3 (growth factor support is permitted)
- Platelets ≥ 100,000/mm3 (may be reached by transfusion)
- Hemoglobin ≥ 10 gm/dl (may be reached by transfusion)
- GPT/GOT and bilirubin < 3 x ULN (or < 5 x ULN in case of liver metastasis)
- Creatinine < 1.5 x ULN

3.1.10 Females of child-bearing potential (FOCBP) and males must agree to use adequate contraception (see Appendix 2) prior to study entry, for the duration of study participation, and for 2 weeks following completion of therapy. Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Likewise, if the female partner of a male patient becomes pregnant while participating in this study, he should inform his treating physician immediately

NOTE: A FOCBP is *any woman* (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not* undergone a hysterectomy or bilateral oophorectomy
- *Has had* menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)

3.1.11 Female patients must have a negative urine pregnancy test within 7 days prior to registration. If urine test is positive, it should be followed by serum pregnancy test.

3.1.12 Patients must sign an informed consent prior to registration and before undergoing any study-specific procedures indicating that they are aware of the investigational nature of this study.

3.1.13 Patient must have the ability to swallow and retain oral medication.

3.1.14 Patient must have the ability to comply with all study requirements.

3.2 Exclusion Criteria

3.2.1 Any uncontrolled neurological symptom attributed to CNS metastasis.

3.2.2 Brain metastasis must not be impending herniation or other significant vasogenic edema requiring increasing steroid doses. Lesions must not have frank hemorrhage.

3.2.3 Patients with leptomeningeal disease are not eligible for participation
Please note: leptomeningeal enhancement is not an exclusion

3.2.4 Any significant medical illnesses or infection that, in the investigator's opinion, cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy are not eligible for participation

3.2.5 Known HIV positive status

3.2.6 Known active Hepatitis B and/or C

3.2.7 Previous treatment with palbociclib

3.2.8 Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to palbociclib are not eligible.
AND/OR
Patients who have had prior exposure to compounds of similar chemical or biologic composition to palbociclib are not eligible hypersensitivity to any component of palbociclib are not eligible for participation.

3.2.9 Female patients who are pregnant or nursing are not eligible.

3.2.10 Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible:

- Ongoing or active infection requiring systemic treatment
- Symptomatic congestive heart failure
- Unstable angina pectoris
- Cardiac arrhythmia: except atrial fibrillation(AF) and supraventricular tachycardia(SVT) that are controlled by medication
- Psychiatric illness/social situations that would limit compliance with study requirements
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

3.2.11 Patients being treated with any other experimental agents/clinical trials are not eligible for participation. If the patient is on any investigational agent, a wash-out period of minimum 2 weeks prior to registration is mandatory for the patient to be eligible for the study.

3.2.12 Patients who are on any prohibited medication (see Section 4.4.1). A wash-out period of minimum 2 weeks prior to registration is mandatory for the patient to be eligible for the study

3.2.13 Inability to swallow capsules, malabsorption syndrome or gastrointestinal disease that severely affects the absorption of study drugs, major resection of the stomach or small bowel, or gastric bypass procedure.

4.0 TREATMENT PLAN

4.1 Overview

Treatment should be started within 7 days of registration. Patients will be treated with palbociclib 125mg PO for 21 days and then 7 days off to complete one cycle of therapy(I cycle=28 days). Treatment cycles will be continued until disease progression or unacceptable toxicity. Patients are permitted to take trastuzumab concurrently. Upon progression, patients will come off study and will be followed for survival and additional therapies. Upon progression, patients will be treated with CNS directed therapy (such as WBRT, SRS, surgery) per treating physician discretion

4.2 Treatment Administration

Table 3

Treatment Administration Summary						
Agent	**Premedication**	**Dose**	**Route**	**Schedule**	**Cycle Length**	**Supportive Therapies**
Palbociclib	None	125 mg	PO	Days 1 through 21, 7 days off afterwards	4 weeks (28 days)	None

4.2.1 Palbociclib

Palbociclib 125mg PO daily for 21 days, then 7 days off. A cycle comprises of a 28 day period.

Patients will self-administer drug. Drug should be taken with food. Patients should be encouraged to take their dose at approximately the same time each day. There are no pre-medications or supportive medications required. Palbociclib capsules should be swallowed whole (no chewing, crushing or opening them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Patient will be given ***a pill diary*** for recording their daily pill intake. This diary will be reviewed by the study Coordinator at every visit. Patients should bring back unused pills and any empty bottles at each visit. The pills will be collected by the coordinator and taken back to the pharmacy for a pill count

4.2.2 Missed doses:

If a patient misses a dose, it can be taken up to 12 hours prior to the next scheduled dose. If the patient vomits after taking the study drug, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. Any skipped or missed doses will be reported to the study coordinator and treating physicians and should be recorded in the pill diary. If a patient misses any 3 doses (may not be consecutive) within one cycle of the treatment, the patient may be discontinued from the study.

4.2.3 In the HER2-positive cohort, patients may be given palbociclib as monotherapy, at the above mentioned dose OR continue/start on trastuzumab as standard of care concurrently with palbociclib
Refer to section for 4.5 for dosing instructions for Trastuzumab.

4.3 Toxicity Management & Dose Delays/Modifications

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table). Toxicity will be assessed according to the NCI CTCAE version 4.03.

Trastuzumab dose modifications will be done per standard of care.

Table 5

Toxicity	Grade/Description	Palbociclib
Hematologic Toxicities		
Neutropenia	Grade 1 or 2	Maintain dose level.
	Grade 3	No dose adjustment is required. Consider repeating complete blood count monitoring within one week. Withhold initiation of next cycle until recovery to Grade ≤2. [I.e. grade 3 neutropenia that corrects to grade 1/2 is acceptable and does not require dose reduction (unless febrile)]
	Grade 3 ANC + Fever ≥38.5ºC and/or infection	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤2 (≥1000/mm3). Resume at next lower dose.
	Grade 4	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤2. Resume at next lower dose.
Thrombocytopenia	Grade 1 or 2	Maintain dose level.
	Grade 3	No dose adjustment is required. Consider repeating complete blood count monitoring within one week. Withhold initiation of next cycle until recovery to Grade ≤2. Dosing can be withheld for a maximum of 28 days
	Grade 4	Withhold palbociclib and initiation of next cycle until recovery to Grade ≤2. Resume at next lower dose.
Non-hematologic Toxicities		
Any	Grade 1 or 2	Maintain dose level.
	Grade ≥ 3 (persisting despite medical treatment)	Withhold until symptoms resolve to(Dosing can be withheld for a maximum of 28 days • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the next lower dose.

Note: Dosing can be withheld for a maximum of 28 days. If dosing cannot be resumed after this period, the drug will be permanently discontinued.

Any required dose reductions should be made according to the dose levels specified in the palbociclib package insert. If dose reductions are required per section 4.3, they should be made according to the following table:

Starting Dose Level	125 mg/per day
Level -1	100 mg/day
Level -2	75 mg/day

4.4 Concomitant Medications and dietary restrictions

Concomitant medications should be recorded from time of registration to the end of study visit.

4.4.1 Prohibited concomitant medications

Patients taking palbociclib should avoid the following medications:

- *CYP3A4 Inhibitors, Inducers and Substrates: See Appendix 3 for a list of* Strong CYP3A4 Inhibitors; Strong and moderate Inducers and Substrates
  (Note: The palbociclib package insert recommends avoidance of strong CYP3A inhibitors and inducers, moderate CYP3A inducers and sensitive CYP3A4 substrates with narrow therapeutic indices. If strong inhibitors cannot be avoided, it is recommended to reduce palbociclib dose to 75mg daily. If the strong inhibitor is discontinued, dose may be increased after 3-5 half-lives of the inhibitor)
- Clozapine
- Dipyrone
- Fusidic Acid
- Natalizumab
- Pimecrolimus
- Tacrolimus
- Tofacitinib

Also, prohibited are:

- lapatinib,
- trastuzumab-emtansine,
- pertuzumab.

4.4.2 Dietary restrictions/prohibited food products

Palbociclib is to be taken with food. However, Grapefruit and grapefruit juice and products containing grape fruit should be strictly avoided. Seville oranges, blood oranges and starfruit should also be avoided.

4.5 Other Modalities or Procedures

Patients may be concomitantly treated with trastuzumab, which is typically given at a loading dose of 8mg/kg IV infused over 90 minutes followed by a maintenance dose of 6mg/kg infused over 30-90minutes every 3 weeks. *Note: if continuing trastuzumab from previous treatment, loading dose should not be administered*

At progression, patients will undergo CNS directed therapy, which may include WBRT; SRS; or NSGY as per treating physician's discretion.

4.6 Duration of Therapy

Patients may continue to receive palbociclib until any of the following occur:

- Disease progression (systemic and/or CNS progression)
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from either study treatment or the as a whole study
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)

4.7 Duration of Follow Up

Patients will have the first follow up visit at 3 months (i.e. 3 months after discontinuation of treatment) at which time the following will be performed:

- CBC with differential
- Assessment of AEs/SAEs
- Physical examination (full physical per SOC)
- Assessment of ECOG performance status
- Concomitant medication review

After this, patients will be followed up at 6, 9 and 12 months, and then every 6 months to a maximum of 3 years to collect survival data. Patients receiving subsequent therapy will be followed and treatment information will be collected.
NOTE: patients who are followed at an outside institution and do not have an oncologist at Northwestern or an affiliated study site may be contacted by the study personnel at these time points to assess vital statistics (alive/dead).

4.8 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study at any time at their own request. Or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment
- Patient withdraws consent
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF). This is defined as 3 attempts, made 1 week apart, to contact patient by preferred method of contact.

4.9 Patient Replacement

If a patient is enrolled in the study but comes off study before cycle 1 day 1 of treatment, the patient may be replaced.

5.0 STUDY PROCEDURES

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9***	**x**	**Follow-up visits**			
Procedure/Study Day	SV (Screening period)[1]	C1D1[2]	C1D15 (±3D)	C2D1 (±3D)	C2D15 (±3D)	C3D1 (±3D)	C4D1 (±3D)	C5D1 (±3D)	C6 and up D1 (+/- 3D)	Off treatment	3M (±1Month)	6M (±1month)	9M (±1 month)	12M + q6M to 3 yrs (±1 month)
Informed Consent	X													
Medical History and eligibility	X													
Palbociclib (21d on, 7d off)[3]		R		R		R	R	R	R					
Trastuzumab (Herceptin) [Optional][3]		Loading dose of 8mg/kg IV infused over 90 minutes; then a maintenance dose of 6mg/kg infused over 30-90minutes q3 weeks. ; If continuing trastuzumab from previous treatment, loading dose should not be administered												
ECHO (For pts on optional Trastuzumab)	X[10]					X[10]			X[10]					
CT chest, abdomen, pelvis; nuclear bone scan[4]	X					X		X	X[4]	X				
MRI brain[4]	X					X		X		X				
Assessment of AEs/SAEs		X	X	X	X	X	X	X	X	X	X	X	x	x
Concomitant medications	X			X		X	X	X	X	X	x	x	x	x
Physical examination, weight & Height[5]	X		X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs						X						X	X	X
Pregnancy test[6]	X													
Serum chemistry[7]	X	X		X		X	X	X	X	X				
CBC with diff	X	X	X	X	X	X	X	X	X	X	X			
Research blood samples		R				R		R						
Archival Tissue sample[8]		R												
Questionnaires[9]		R				R		R						

NU 15B08

X=Standard of Care; R=Research

1 Screening period=28 days, unless otherwise specified for certain tests.

2Treatment (D1) should occur within 7 days of registration.(*Note; On C1D1 patients will be required to take an appointment with the treating physician wherein vitals will be taken and patient will be assessed for any AEs)*

3 Continue 28 day palbociclib cycle until PD or toxicity
Patients may receive concurrent trastuzumab every 3 weeks per standard dosing.

4 Repeat every 56 days.

5 Every physical exam will be a full physical exam and is standard of care. Height will be measured only at baseline.

6 If pre or perimenopausal: Urine test within 7 days of registration. If urine positive, to be followed by serum pregnancy test.

7 Serum Chemistry will include calcium, chloride, creatinine, sodium, potassium, blood urea nitrogen, bicarbonate, glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, and total protein. This is to be conducted within 14 days prior to Day1

8 Genotyping of CNS and non-CNS tumors will be performed from available tissue. Genotyping will be performed through commercial next generation sequencing assays.

9 Cognitive function will be assessed at C1D1, C3D1and C5D1, will be collected using the Functional Assessment of Cancer Therapy-Cognitive Function version 3.0 (FACT_Cog, ver 3.0. Quality of life measures will be measured by Functional Assessment of Cancer Therapy-Brain (FACT-Br) Version 4 Both questionnaires are to be completed before dosing. The questionnaires are required to be completed by the patient, under the supervision of the study coordinator

10 Patients who undergo treatment with trastuzumab must have standard of care monitoring (SOC) with an echocardiogram every 3 months (an echocardiogram 3 months preceding the first dose of trastuzumab while on study will be accepted). Dose adjustments will also be done per SOC

6.0 ENDPOINT ASSESSMENT

6.1 Definitions

6.1.1 Measurable Lesions

CNS lesions must be accurately measured in at least one dimension (greatest diameter) with a ***minimum size of 5mm by MRI.*** Systemic lesions will be accurately measured in at least one dimension (greatest diameter) with a minimum size of 10mm by CT imaging. Bone scans will be used to assess bone metastasis.

6.1.2 Non-measurable Lesions

Defined as all other lesions less than 10mm. Examples of non-measurable lesions include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, and lymphangitic involvement of skin or lung.

6.1.3 Response criteria

The Modified RANO-BM criteria

(NOTE: The modification is based on the grounds that RANO-BM uses a size criteria requiring >=10mm, whereas this study will allow a size of >=5mm (MRI will use 1.5mm slices or less).

Table 6

Category	Description
Complete Response (CR)	Disappearance of all lesions.
Partial Response(PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease(PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
Stable Disease(SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.2 Primary Endpoint

The primary endpoint of this study to assess the radiographic response rate in the CNS by **modified** Response Assessment in Neuro-Oncology Criteria Brain Metastasis (modified RANO-BM) (20)(refer Section 6.1.3).

Any patient who has completed at ***least 2 cycles*** of treatment will be evaluable for this endpoint

6.3 Secondary Endpoints

1. Secondary endpoints include PFS and OS, where PFS is defined as the time from treatment initiation to documented disease progression, and OS is defined as the time from treatment initiation until death due to any cause.
   Any patient who has completed at ***least 2 cycles*** of treatment will be evaluable for this endpoint

2. Time to CNS progression will be defined as the time from treatment initiation to documented disease progression (modified RANO-BM criteria) in the CNS.
   Any patient who has completed at ***least 2 cycles*** of treatment will be evaluable for this endpoint

3. Systemic ORR (defined as PR or CR) will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (23).
   Any patient who has completed at ***least 2 cycles*** of treatment will be evaluable for this endpoint

4. The number, frequency, and severity of adverse events (as defined by the NCI CTCAE version 4.03) will be recorded.
   Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints

6.4 Exploratory Endpoints

1. Circulating tumor DNA will be collected from whole blood at baseline, 2 and 4 months through commercial next generation sequencing assays. A sample of 20ml whole blood will be collected and processed as described in Section 9.0
2. Genotyping of CNS and non-CNS tumors will be performed from archival tissue that will be obtained at baseline. Genotyping will be performed through commercial next generation sequencing assays.
3. Patient reported outcome questionnaires:

   Cognitive function will be assessed at C1D1, C3D1and C5D1 and will be collected using the Functional assessment of Cancer Therapy-Cognitive function Version 3.0 (Fact –Cog) (available as stand-alone document)

   Quality of life measures will be assessed at C1D1, C3D1, C5D1 and will be measured by Functional Assessment of Cancer Therapy-Brain (FACT-Br) Version 4.0 (available as stand-alone document)

   The questionnaires will be completed by the patient under the supervision of the study coordinator

   .

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (http://cancer.northwestern.edu/CRO/data/DataandSafetyMonitoringPlanMay2014.pdf). The level of risk attributed to this study requires high level monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is *life-threatening*.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- **Results in *persistent or significant disability or incapacity*.**
- **Is a *congenital anomaly/birth defect.***
- **Is an *important medical event*.**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP (http://cancer.northwestern.edu/CRO/data/DataandSafetyMonitoringPlanMay2014.pdf)

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any <u>death of an NU subject</u> that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB <u>within 24 hours of notification</u>. Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment
- Any <u>death of a non-NU subject</u> that is unanticipated and at least possibly related and <u>any other UPIRSOs</u> will be reported to the NU IRB <u>within 5 working days of notification</u>.
- All <u>other deaths of NU subjects</u> not previously reported, <u>other non-NU subject deaths</u> that were unanticipated and unrelated, and <u>any other</u>

SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.3.3 Reporting to the FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

.

7.3.3.4 Reporting to Pfizer

All SAEs, regardless of attribution, occurring during the study or within 30 days of the last administration of study drug must be reported to the PI upon discovery or occurrence, within 24 hours. Additionally, the investigator or qualified designee must complete the Pfizer SAE Form and send it electronically to Pfizer contact Manali.Talathi@pfizer.com

8.0 DRUG INFORMATION

8.1 Palbociclib

8.1.1 Other names

Ibrance

8.1.2 Classification – cyclin-dependant kinase inhibitor

8.1.3 Mode of action

Palbociclib is a reversible small molecule cyclin-dependent kinase (CDK) inhibitor which is selective for CDK 4 and 6. CDKs have a role in regulating progression through the cell cycle at the G1/S phase by blocking retinoblastoma (Rb) hyperphosphorylation. Palbociclib reduces proliferation of breast cancer cell lines by preventing progression from the G1 to the S cell cycle phase.

8.1.4 Storage and stability

All investigational products should be kept in a secure and dry place. Drug is to be stored at 20^{o}C to 25^{o}C (68^{o}F to 77^{o}F); excursions are permitted between 15^{o}C to 30^{o}C (59^{o}F to 86^{o}F)

8.1.5 Protocol dose specifics

Palbociclib 125mg PO daily for 21 days, then 7 days off

8.1.6 Preparation

No preparation is required.

8.1.7 Route of administration for this study

Oral. It is to be taken with food, except grapefruit and grapefruit products. Seville orange, blood orange and star fruit should also be avoided. The capsule is be swallowed as whole.

8.1.8 Incompatibilities

Please refer to Sections 4.4

8.1.9 Availability & Supply

Palbociclib (commercial) will be supplied by Pfizer.
It will be supplied in bottles of 21 capsules. One bottle of 21 capsules will be dispensed to the patient at the beginning of each cycle. Contact for drug supply is Manali Talathi, email: Manali.Talathi@pfizer.com. A drug order form is available as stand- alone document.

Table 7

Package Configuration	**Capsule Strength(mg)**	**Route**	**Capsule Description**
Bottles of 21 capsules	125	Oral	opaque, hard gelatin capsules, size 0, with caramel cap and body, printed with white ink “Pfizer” on the cap, “PBC 125” on the body
Bottles of 21 capsules	100	Oral	opaque, hard gelatin capsules, size 0, with caramel cap and body, printed with white ink “Pfizer” on the cap, “PBC 100” on the body
Bottles of 21 capsules	75	Oral	opaque, hard gelatin capsules, size 0, with caramel cap and body, printed with white ink “Pfizer” on the cap, “PBC 75” on the body

8.1.10 Side effects

8.1.10.1 : Palbociclib

(***Note:*** *side effects are based on studies evaluating palbociclib use in combination with letrozole)*

Most Likely

- Central nervous system: Fatigue (41%; grade 3/4: 2%), peripheral neuropathy (13%)
- Dermatologic: Alopecia (22%)

- Gastrointestinal: Nausea (25%; grade 3: 2%), stomatitis (25%), diarrhea (21%; grade 3: 4%), decreased appetite (16%; grade 3: 1%), vomiting (15%)
- Hematologic & oncologic: Abnormal absolute lymphocyte count (81%; grade 3: 17%; grade 4: 1%; decreased lymphocytes), neutropenia (75%; grade 3: 48%; grade 4: 6%), leukopenia (43%; grade 3: 19%), anemia (35%; grade 3: 5%; grade 4: 1%), thrombocytopenia (17%; grade 3: 2%)
- Infection: Infection (55%; grade 3/4: 5%)
- Neuromuscular & skeletal: Weakness (13%; grade 3: 2%)
- Respiratory: Epistaxis (11%)

Less Likely

- Cardiovascular: Pulmonary embolism (4% to 5%)
- Respiratory: Upper respiratory tract infection (31%; grade 3: 1%)

8.1.10.2 Palbociclib plus Trastuzumab

The risks associated with this combination therapy are unknown. Trastuzumab is considered to be a well-tolerated drug that does not increase toxicity of companion therapies (see Background Section 1.1.6). Thus, HER-2 positive patients may concurrently receive trastuzumab as standard of care .The standard dose outlined in Section 4.2 and 4.5
(*Note: Drug accountability m e a s u r e s will be done according to NM Investigational Pharmacy Standard Operating Procedures*.)

8.1.11 Nursing implications

Patients will *self-administer* drug. These instructions should be clearly communicated to the patient.

- Drug should be taken with food.
- Patients should be encouraged to take their dose at approximately the same time each day.
- There are no pre-medications or supportive medications required.
- If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.
- Patient will be given ***a pill diary*** for recording their daily pill intake. This diary will be reviewed by the study Coordinator at every visit.
- Any skipped or missed doses will be reported to the study coordinator and treating physicians and should be recorded in the pill diary
- Palbociclib capsules should be swallowed whole (no chewing, crushing or opening them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.
- Patients should be instructed to inform the PI about any signs or symptoms they experience which are different and/or exceeds their normal levels.

- Patient should be counseled to avoid grapefruit and grapefruit juice, Seville oranges and blood oranges, and star fruit (See section 4.4 2)

8.1.12 Return and Retention of Study Drug

All unused investigational products will be returned to a Pfizer-authorized depot or disposed of upon authorization by Pfizer according to the investigational site policy.

8.2 Trastuzumab (Herceptin)

This is an FDA approved drug and is used as standard of care for HER2-positive breast cancer patients. It is a recombinant humanized monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2). After binding to HER2 on the tumor cell surface, trastuzumab induces an antibody-dependent cell-mediated cytotoxicity against tumor cells that overexpress HER2. HER2 is overexpressed by many adenocarcinomas, particularly breast adenocarcinomas.

Dose: A loading dose of 8mg/kg IV infused over 90 minutes followed by a maintenance dose of 6mg/kg infused over 30-90minutes every 3 weeks. *Note: if continuing trastuzumab from previous treatment, loading dose should not be administered*.

Trastuzumab will be given as standard of care therapy. If patient is enrolled in the study and prefers to take their trastuzumab doses in an institution other than the one where they are undertaking this study treatment (palbociclib), they would follow the same standard of care dosing as outlined above.

9.0 CORRELATIVES/SPECIAL STUDIES

9.1 Sample Collection Guidelines

Research blood samples will be collected at baseline and 2 months and 4 months from treatment initiation. 20 mL of whole blood should be collected in two 10mL plastic lavender top tubes (K2EDTA), which will be used for commercial genotyping.. All blood samples will be shipped at room temperature to NU PCF-CTUwithin 24hr of blood draw. If, for some reason, blood is not shipped within 24 hours, it may be stored at -80 degrees Celsius and shipped at the next possible date. Study coordinators will keep an account of all samples that are collected and shipped.

A formalin fixed paraffin embedded (FFPE) tumor tissue sample or newly obtained formalin fixed biopsy of a tumor lesion (not previously irradiated) will be procured. This may be CNS or non-CNS systemic tumor tissue. At a later date (to be specified by the PI), these samples will be shipped by NU PCF-CTU to Foundation medicine for commercial genotyping. Foundation Medicine requires 40 microns of tissue for analysis. This can be done either as 10 slides cut at 4 microns or 8 slides cut at 5 microns.

Any Extra blood or tissue samples will remain at Northwestern University's Path Core for future research use.

Please refer to the laboratory manual for further details

9.2 Sample Processing, Storage, and Shipment

Blood samples will be collected at room temperature and sent to NU PCF-CTU within 24 hours.

Pathology Core-Clinical Trials Unit
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
710 N. Fairbanks Ct, Olson 8-415
Phone: 312.908.0603
Fax: 312.503.2792
PCF-CTU@northwestern.edu

(Note: The samples will be processed and stored here until it is shipped to Guardant Health at a later date which is to be specified by the PI).

Please refer to the laboratory manual for further details (including availability of sample collection kits).

FFPE samples of available CNS and non-CNS tissue will be sent to NU PCF-CTU
Pathology Core-Clinical Trials Unit
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
710 N. Fairbanks Ct, Olson 8-415
Phone: 312.908.0603
CTUtissuerequests@northwestern.edu

(Note: The samples will be stored here until it is shipped to Foundation Medicine at a later date which is to be specified by the PI).

Please refer to the laboratory manual for further details.

9.3 Assay Methodology

Qiagen circulating nucleic acid kit will be used for extraction of ctDNA from plasma. QuickExtract formalin fixed paraffin embedded (FFPE). DNA Extraction kit will be used for extraction of DNA from tumor FFPE samples from CNS and non-CNS samples. Commercially available primers (Guardant Health, Foundation Medicine) will be used to amplify exonic regions. Specifically, the Guardant Health assay for ctDNA will evaluate a 68 gene panel and the Foundation Medicine assay for FFPE samples will evaluate a 315 gene panel; both include CCND1, CCND2, CDK4, CDK6, CDKN2A. The amplification protocol is optimized for use on degraded products such as ctDNA and FFPE samples. Amplification products will then be used in modified indexed Illumina library prep protocol for adapter ligation in preparation for sequencing on HiSeq. Libraries will be sequenced on a HiSeq using a 2x150 protocol. At least 100X coverage will be obtained from 90% of regions sequenced to ensure potential detection of rare mutations in ctDNA and in tumor biopsy DNA.

9.4 Specimen Banking

This is optional.

As stated above, blood samples and FFPE samples of available CNS and non-CNS tissue will be sent to NU PCF-CTU and later to Guardant Health and Foundation medicine

respectively. *Any extra blood or tissue samples will remain at Northwestern University's Path Core for future research use. This should be clearly stated in the consent form and communicated to the patient.*

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This will be a single arm phase 2 study enrolling patients with metastatic HER2-positive breast cancer who have asymptomatic brain metastasis.. Patients will be treated with 125mg of PO palbociclib (21 days on, 7 days off), and MRI of the brain will monitor for disease progression. Upon progression patients will be treated with local CNS directed therapy (such as WBRT, SRS, surgery) per treating physician discretion.

The **primary endpoint** of this study to assess the radiographic response rate in the CNS by modified RANO-BM criteria.

Secondary endpoints include PFS and OS, where PFS is defined as the time from treatment initiation to documented disease progression, and OS is defined as the time from treatment initiation until death due to any cause. Time to CNS progression will be defined as the time from treatment initiation to documented disease progression in the CNS. Systemic ORR (defined as PR or CR) will be assessed by RECIST Version 1.1 (23). The number, frequency, and severity of adverse events (as defined by the NCI CTCAE version 4.03) will be recorded.

Exploratory endpoints include circulating tumor DNA will be collected from whole blood at baseline, 2 months, and 4 months through commercial next generation sequencing assays. Genotyping of CNS and non-CNS tumors will be performed from available tissue that will be obtained at baseline. Genotyping will be performed through commercial next generation sequencing assays. Cognitive function will be assessed at C1D1, C3D1, C5D1 and will be collected using the FACT-Cog; and, quality of life with the FACT-Br.

10.2 Sample Size and Accrual

A one sample Bayesian design for the primary endpoint of ORR will be used

, It is hypothesized that the current response rate of 23% will increase to 40% by treatment with palbociclib. A prior beta distribution with shape parameters 0.75 and 0.50 is selected so that the prior probability that the response rate exceeds 23% is 80%. A sample of 20 HER-2 patients will be observed, and based on the number of responses out of20, the posterior probability that the response rate is greater than 40% will be calculated, with the goal that this probability be at least 80%. If 10/20 responses are seen, there is a 83% chance that the true response rate exceeds 40%.

Posterior probabilities may be calculated for any desired true response rate and for any number of observed responses.

10.3 Data Analyses Plans

The primary analysis will be on the intent-to-treat (ITT) population, including all evaluable patients. Response rates will be assessed by modified RANO-BM, where lesions of 5mm or more will be allowed (20). Maximum response prior to disease progression will be used. The response rate will be estimated by the proportion of overall response, and its 80% confidence interval (CI) and 95% CI will be estimated using the exact binomial distribution.

PFS is defined as the time from treatment initiation to documented disease progression. OS is defined as the time from the start of treatment until death due to any cause. For patients alive at the time of data cut-off, PFS and OS will be censored as of the last tumor assessment date or known to be alive, respectively. The PFS and OS will be estimated using the Kaplan-Meier method. Time to CNS progression will be defined as the time

from treatment initiation to documented disease progression in the CNS will be evaluated using the Kaplan-Meier method as well. Systemic ORR (defined as PR or CR) will be assessed by RECIST Version 1.1, and estimated by the proportion of overall response, and its 80% CI and 95% CI will be estimated using the exact binomial distribution. In addition, Bayesian posterior probabilities will be calculated. The number, frequency, and severity of adverse events (as defined by the NCI CTCAE version 4.03) will be recorded.

Whole blood will be used to assess ctDNA and mutational profiles. Cyclin and CDK gene abnormalities will used as a dichotomous variable (aberrant versus not aberrant) to predict clinical benefit or overall response rates using appropriate statistical summaries. Cox proportional hazards regression will be used to compare how these biomarkers are associated with PFS and OS as well.

Descriptive statistics will be used to assess changes in genomic landscape using ctDNA at baseline, 2 and 4 months. Genomic landscapes will be described in available CNS and non-CNS tissue to evaluate for concordance in mutational profiles.

Cognitive function and quality of life measures will be scored and summarized using descriptive statistics, and changes from baseline, 2 and 4 months will be described with nonparametric Wilcoxon rank sum tests or t tests as appropriate (20). The frequency of missing values at each time point will also be reported. If data on clinically meaningful changes on the cognitive function are available, we will also describe the changes according to whether the patient “improved” or “declined”.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient’s participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Pfizer. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

Registering a Patient to the Phase II
BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Eligibility eCRF (complete in NOTIS)
- Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)
- Signed and dated informed consent document (upload in NOTIS)
- Pathology Report (upload in NOTIS)

The QAM will review the registration, register the patient, assign an identification number, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

.

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document).
. Generally, for all phase II patients, data are due at the end of every cycle.

11.5 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.
- Draft informed consent form should for review/approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

11.6 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires high level monitoring, as outlined in the DSMP (http://cancer.northwestern.edu/CRO/data/DataandSafetyMonitoringPlanMay2014.pdf)

The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the Appendices for additional data submission instructions.

11.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.7.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.8 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.9 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. . For trials that require high intensity monitoring, the assigned QAM will prepare a preliminary data summary (to be approved by the DMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is

approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2014. Atlanta: American Cancer Society; 2014.
2. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52. Epub 2000/08/30. doi: 10.1038/35021093. .
3. Arvold ND, Oh KS, Niemierko A, et al. Brain metastases after breast-conserving therapy and systemic therapy: incidence and characteristics by biologic subtype. Breast cancer research and treatment. 2012;136(1):153-60. doi: 10.1007/s10549-012-2243-x.
4. Tsukada Y, Fouad A, Pickren JW, et al. Central nervous system metastasis from breast carcinoma. Autopsy study. Cancer. 1983;52(12):2349-54.
5. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(2):134-41. doi: 10.1200/JCO.2010.30.1655.
6. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. Jama. 1998;280(17):1485-9.
7. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322(8):494-500. doi: 10.1056/NEJM199002223220802.
8. Alexander E, 3rd, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. Journal of the National Cancer Institute. 1995;87(1):34-40.
9. Flickinger JC, Kondziolka D, Lunsford LD, et al. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. International journal of radiation oncology, biology, physics. 1994;28(4):797-802.
10. Pirzkall A, Debus J, Lohr F, et al. Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1998;16(11):3563-9.
11. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004;363(9422):1665-72. doi: 10.1016/S0140-6736(04)16250-8.
12. Lin NU. Breast cancer brain metastases: new directions in systemic therapy. Ecancermedicalscience. 2013;7:307. doi: 10.3332/ecancer.2013.307.
13. 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(11):1427-38.
14. 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(1):25-35. doi: 10.1016/S1470-2045(14)71159-3.
15. Michaud K, Solomon DA, Oermann E, et al. Pharmacologic inhibition of cyclin-dependent kinases 4 and 6 arrests the growth of glioblastoma multiforme intracranial xenografts. Cancer research. 2010;70(8):3228-38. doi: 10.1158/0008-5472.CAN-09-4559.
16. Barton KL, Misuraca K, Cordero F, et al. PD-0332991, a CDK4/6 inhibitor, significantly prolongs survival in a genetically engineered mouse model of brainstem glioma. PloS one. 2013;8(10):e77639. doi: 10.1371/journal.pone.0077639.
17. Raub TJ, Wishart GN, Kulanthaivel P, et al. Brain Exposure of Two Selective Dual CDK4 and CDK6 Inhibitors and the Antitumor Activity of CDK4 and CDK6 Inhibition in Combination with Temozolomide in an Intracranial Glioblastoma Xenograft. Drug metabolism and disposition: the biological fate of chemicals. 2015;43(9):1360-71. doi: 10.1124/dmd.114.062745.
18. de Gooijer MC, Zhang P, Thota N, et al. P-glycoprotein and breast cancer resistance protein restrict the brain penetration of the CDK4/6 inhibitor palbociclib. Investigational new drugs. 2015. doi: 10.1007/s10637-015-0266-y.
19. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. The Lancet Oncology. 2015;16(6):e270-8. doi: 10.1016/S1470-2045(15)70057-4.

20. Reeve BB, Hays RD, Bjorner JB, et al. Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). Medical care. 2007;45(5 Suppl 1):S22-31. doi: 10.1097/01.mlr.0000250483.85507.04.
21. McClendon AK, Dean JL, Rivadeneira DB, Yu JE, Reed CA, Gao E, et al. CDK4/6 inhibition antagonizes the cytotoxic response to anthracycline therapy. Cell cycle. 2012;11(14):2747-55.
22. Horiuchi D, Kusdra L, Huskey NE, Chandriani S, Lenburg ME, Gonzalez-Angulo AM, et al. MYC pathway activation in triple-negative breast cancer is synthetic lethal with CDK inhibition. The Journal of experimental medicine. 2012;209(4):679-96.
23.. Roberts PJ, Bisi JE, Strum JC, Combest AJ, Darr DB, Usary JE, et al. Multiple roles of cyclin-dependent kinase 4/6 inhibitors in cancer therapy. Journal of the National Cancer Institute. 2012;104(6):476-87.
24.. Vidula N, Rugo HS. Cyclin-Dependent Kinase 4/6 Inhibitors for the Treatment of Breast Cancer: A Review of Preclinical and Clinical Data. Clinical breast cancer. 2015.
25. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-92.
26. von Minckwitz G, du Bois A, Schmidt M, Maass N, Cufer T, de Jongh FE, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(12):1999-2006.
27. Powell C, Guerrero D, Sardell S, Cumins S, Wharram B, Traish D, et al. Somnolence syndrome in patients receiving radical radiotherapy for primary brain tumours: a prospective study. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2011;100(1):131-6.
28. Chin LS, Lazio BE, Biggins T, Amin P. Acute complications following gamma knife radiosurgery are rare. Surgical neurology. 2000;53(5):498-502; discussion
29. Werner-Wasik M, Rudoler S, Preston PE, Hauck WW, Downes BM, Leeper D, et al. Immediate side effects of stereotactic radiotherapy and radiosurgery. International journal of radiation oncology, biology, physics. 1999;43(2):299-304.
30 . Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. The Lancet Oncology. 2009;10(11):1037-44.

12.0 APPENDICES

APPENDIX 1

ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

APPENDIX 2

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
• Male condom plus spermicide • Cap plus spermicide • Diaphragm plus spermicide	• Copper T • Progesterone T • Levonorgestrel-relasing	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

NOTE: choice of contraception should be discussed with primary treating oncologist to discuss the risks and benefits of different modalities of contraception. Abstinence is not an acceptable method

Appendix 3

Strong CYP3A4 Inhibitors*	**Strong CYP3A4 Inducers***	**CYP3A4 Substrates***
Indinavir Ritonavir Clarithromycin Itraconazole Ketoconazole Nefazodone Conivaptan Boceprevir Lopinavir mibefradil Nelfinavir Posaconazole Saquinavir Telaprevir Telithromycin Voriconazole Grapefruit juice	Rifampin Carbamazepine Phenytoin St. John's Wort **Moderate CYP3A4 Inducers*** Bosentan Efavirenz Etravirine Modafinil Nafcillin	Aprepitant Budesonide Conivaptan Darifenacin Darunavir Dasatinib Eletriptan Eplerenone Everolimus Fluticasone Midazolam Triazolam Diazepam Alprazolam Lovastatin Simvastatin Atorvastatin Felodipine Buspirone Sildenafil Tadalafil Tacrolimus Cyclosporine Sirolimus Clarithromycin Erythromycin Trazodone Haloperidol Imatinib Carbamazepine Vincristine Tamoxifen Tolvaptan
*This list is not all inclusive. for more information, please refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm		

13.0 HISTORY OF AMENDMENT SUMMARY OF CHANGES

Amendment 1 –May 20, 2016			
Sections(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Title page	Included email addresses and department for each northwestern physician	Removed email addresses and department for all northwestern university Sub-Investigator Added : Valerie nelson, MD as Sub-Investigator from Northwestern Lake Forest Hospital	***To accommodate all content on one page. All email addresses are available in the northwestern outlook system***
Study Schema	No previous WBRT	Any WBRT must have occurred >6 months ago	***Per PI, to be consistent with change in inclusion criteria 3.1.8***
Study summary and Inclusion criteria 3.1.5	ECOG ≥2	ECOG≤2	***Error correction***
Inclusion criteria 3.1.1	Histologically confirmed triple negative or HER2-positive metastatic breast cancer (estrogen and progesterone receptor 0%, HER-2 3+ by immunohistochemistry. If IHC score of 2, FISH ratio must be greater than 2.0. If FISH less than 2.0, HER2 copy number must be greater than 6. NOTE: Brain lesions are not required to have pathologic confirmation.	**Added note:** HER2-positive patients should also be ER-negative)	***For clarification***
Inclusion 3.1.2	Patients should not have received >2 lines of chemotherapy for metastatic disease	This criteria was removed	***Per PI***
Inclusion criteria 3.1.8	Patients who underwent neurosurgery (NSGY), or stereotactic radiosurgery (SRS) to a brain lesion must	***Added :*** *Whole brain radiation therapy (*WBRT) as well. Any WBRT must have occurred>6 months ago.	***Per PI And QA***

	have a new measureable lesion. NOTE: SRS may be done to a lesion that will not be used for response evaluation and should be done > 2 weeks prior .Any NSGY procedure must have been completed >3 weeks prior to registration. Any NSGY procedure must have been completed >3 weeks prior to registration	Previously surgically excised lesion/tumor bed, may be used as a measurable lesion if disease has progressed since surgery ***Also, added*** Any NSGY procedure must have been completed >3 weeks prior to registration ***and baseline imaging***.	
Section 4.3 Toxicity Management & Dose Delays/Modifications	Table 5 has dose modifications for Palbociclib wit mention of dose reduction.	A table for dose reduction is added just below Table 5 describing the 2 levels of dose reduction(100mg and 75mg) that are allowed	***For clarity. (A clarification memo was earlier sent out for this).***
Section 5.0 Study procedures	In column 9* Dn+28(+/-3D)	Replaced with C6 and up D1(+/-28days) Added an 'X to Column 9 visit ,to indicate that CT chest of abdomen, pelvis,nuclear bone scan is to be done every 56 days	***For clarity***
Section 5.0 Study procedures	ECOG performance status was not indicated in C1D1	ECOG performance status was included in C1D1	***Correction of error***
Section 5.0 Study procedures Footnote 2	Footnote indicated: treatment (D1) should occur within 7 days of registration.	.Added: (Note; On C1D1 patients will be required to take an appointment with the treating physician wherein vitals will be taken and patient will be assessed for any AEs)	***For clarity***
Section 9.0 Correlatives	Blood samples were to be shipped to Guardant Health. Tissue samples were to be shipped to foundation medicine	Blood and tissue samples are to be shipped to Northwestern university Pathology Core – Clinical trial Unit (NU PCF-CTU).The samples will be stored here till the PI indicates that they can be shipped to	***Due to logistical and sub-contract issues.***

		Guardant health and Foundation Medicine. Language has been included in the protocol with correct address for PCF-CTU along with reference to laboratory manual for detailed information.	
Amendment 2–August 2, 2016			
Sections(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Study Schema **Section 3.1.7**	Any WBRT must have occurred >6 months ago	Any WBRT must have occurred >60 days ago	***Per PI*** ***In order to improve accrual***
Section 3.1.1 Inclusion criteria	Histologically confirmed triple negative or HER2-positive metastatic breast cancer (estrogen and progesterone receptor 0%, HER-2 3+ by immunohistochemistry. If IHC score of 2, FISH ratio must be greater than 2.0. If FISH less than 2.0, HER2 copy number must be greater than 6. NOTE: Brain lesions are not required to have pathologic confirmation. ***(Note; HER2-positive patients should also be ER-negative)***	***Removed ;*** *HER2-positive patients should also be ER-negative.*	***Per PI*** ***In order to allow for ER+ disease.*** ***The goal is to improve accrual***

Amendment 3–January 11, 2017			
Sections(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Protocol cover page	Affiliate site :TBD	Houston Methodist Hospital/Houston Methodist Cancer Center added as Affiliate site. PI: Jenny Chang, MD Contact information added	***Houston Methodist Hospital came on board as Affiliate site.***
Throughout	Single center	Changed to Multi-center	***Addition of affiliate site***
Section 3.0 Patient eligibility	Northwestern University RHLCCC as single center Stated that patients should be referred to lead PI Dr.Santa-Maria	Northwestern University as lead site and Coordinating center. Houston Methodist Hopsital as affiliate site. Added language that patients may be referred to the local PI at each participating site as well.	***Houston Methodist Hospital came on board as Affiliate site.***

Amendment 4–January 30, 2017			
Sections(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Throughout	Triple negative breast cancer patients	Removed: language referring to Triple negative breast cancer patients	***Removal of Triple Negative breast cancer cohort from the study. PI wants a more homogenous population with just HER2-positive.No TNBC enrolled so far in the study.***
Study schema	Cohort A(TNBC) and B Cohort B(Her-2 positive) with details	Removed Cohort language. Only Her2-positive patients and related details.	***To be in alignment with removal of TNBC patients from the study.***
Study schema and summary	single-center	Updated to Multi-center. This was previously omitted in error	***Affiliate site was added in the previous amendment.***
Study summary	Sample size: Maximum accrual 33 patients and Evaluable patients: 30 (15 each for TNBC and HER2 positive) Key Inclusion criteria: Trastuzumab allowed for Her2-positive patients	Maximum accrual 25 patients and Evaluable patients: 20 (Her-2 positive) Key Inclusion criteria: Modified to : Trastuzumab allowed for Her2-positive patients. Statistical details updated to align with the current change in sample size and	***In order to align with the current change in patient population to include only HER2-positive patients in the study.***

	Statistical details tailored to the previous sample size and 2 cohorts. A Bayesian probability was to be calculated after the response status in 15 patients has been assessed.	patient population. A Bayesian probability will now be calculated after the response status in 20 patients has been assessed.	
Section 2.0	Primary and secondary objectives had TNBC patients	Removed all language referring to TNBC patients.	***For consistency. In order to align with the current change in patient population to include only HER2-positive patients in the study.***
Section 3.0 Patient eligibility	Language referring to TNBC patients	Removed all language referring to TNBC patients Modified language: sample size numbers upadted. Added langauge: " once all sites are up and running"	***For consistency and to align with current upadtes to the protocol.***
Section 3.1.1 Inclusion criteria	TNBC language	Removed all language referring to TNBC patients Added: ER-positive patients are allowed. Removed other contradictotory language	***For clarity and consistency***
Section 3.1.8 Inclusion criteria	Patients must not have received systemic therapy within 2 weeks of initiating palbociclib. It also had a note stating that Her2-positive patients can remain onTrastuzumab .	This part of the note has been modified to state that : "Patients on trastuzumab can remain on the drug if previously taking, or may start if not. No break or washout period required. Patients with ER-positive disease may not concurrently take endocrine therapy, however, no washout is required if they were previously on endocrine therapy."	***For clarity and consistency***

Section 4.1 Treatment plan overview	TNBC language and statement that HER2-positive patients can take trastuzumb.	Removed all language referring to TNBC patients and restated that patients are permitted to take Trastuzumab(meaning HER2 patients), since they are the only patients to be currently enrolled in the study.	***For clarity and consistency***
Section 10.2 Statistics sample size and accrual	Previous statistical details	Statistical details updated to tailor to the new cohort of HER-2 positive patients(alone) that will be enrolled in the study. Briefly, it states that: "A prior beta distribution with shape parameters 0.75 and 0.50 is selected so that the prior probability that the response rate exceeds 23% is 80%. A sample of 20 HER-2 patients will be observed, and based on the number of responses out of20, the posterior probability that the response rate is greater than 40% will be calculated, with the goal that this probability be at least 80%. If 10/20 responses are seen, there is a 83% chance that the true response rate exceeds 40%."	***In order to align with the current change in patient population to include only HER2-positive patients in the study.***
Amendment 5–August 15, 2017			
Sections(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Title page ***and Section 3.0***	Cesar Santa-Maria, MD as PI	Removed Dr.Santa-Maria and added Massimo Cristofanili, MD as PI with all required contact information	***Dr.Santa-Maria is leaving Northwestern University and is handing over the study to Dr.Cristofanilli***

NU 15B08

Section 3.0 ***Patient eligibility***	TNBC also listed as target population	Removed TNBC	***Correction of error. TNBC was removed from this protocol in an earlier amendment***.
Section 3.2.3 Exclusion criteria	Patients with leptomeningeal disease are not eligible for participation	Added a note to state that : "leptomeningeal enhancement is not an exclusion."	***For increased clarity***
Section 1 Introduction and Background/ Rationale and Reference section	List of references, including ones for TNBC	Removed all references pertaining to TNBC. Re-numbered other references accordingly.	***TNBC was removed from this protocol in an earlier amendment***