Winship Protocol #: Winship 4472-18

Title: A Phase II Multi-institutional Study of Concurrent Radiotherapy, Palbociclib, and Hormone Therapy for Treatment of Bone Metastasis in Breast Cancer Patients

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STUDY SCHEMA

Overall Description: This is a Phase II multi-institutional study to evaluate the efficacy and safety of palbociclib and hormone therapy during conventionally fractionated radiotherapy for bone metastases in hormone receptor positive, her2/neu negative breast cancer patients.

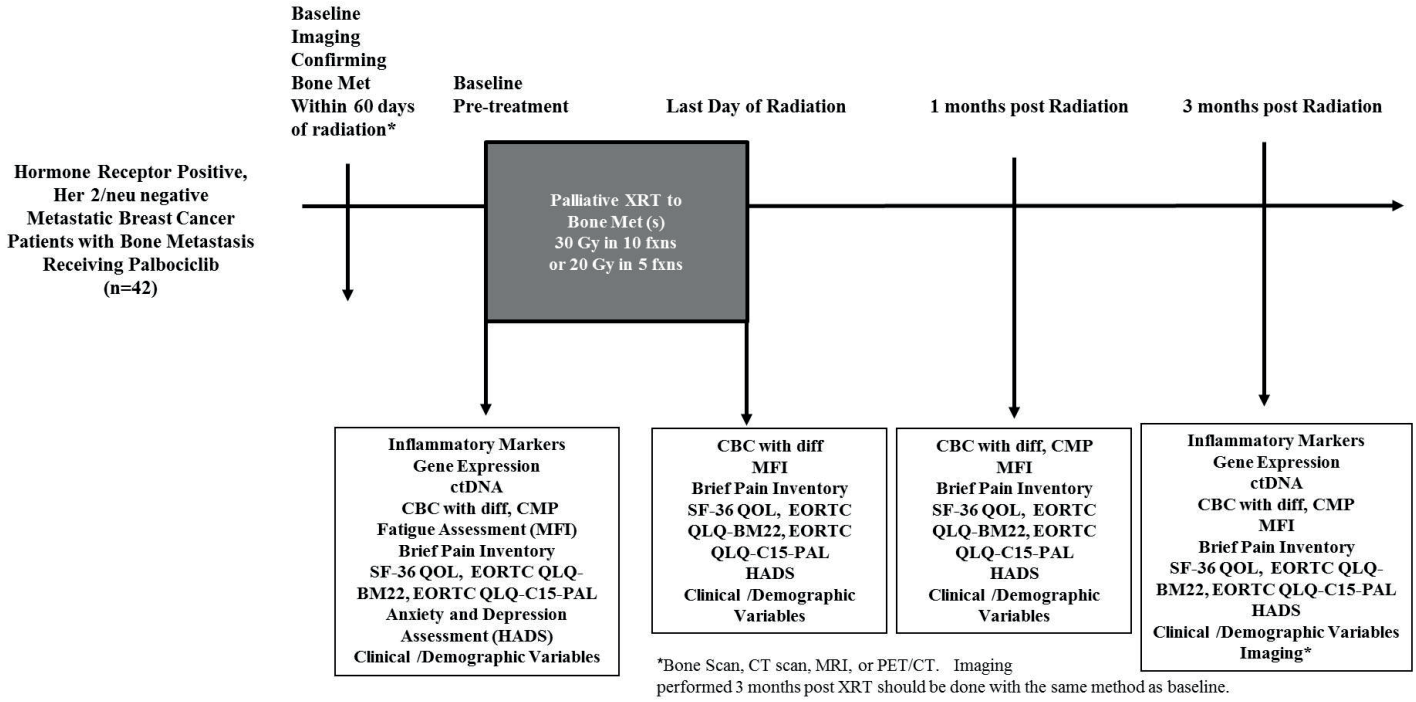

Figure 1. Study Schema

Met-metastasis; ctDNA – circulating tumor DNA; CBC with diff – complete blood count with differential; CMP – complete metabolic panel; MFI – Multidimensional fatigue Inventory; QOL – Quality of Life; EORTC QLQ-BM22 – European Organization for Research and Treatment of Cancer Metastases Module; EORTC QLQ-C15-PAL - EORTC Quality of Life Questionnaire Core 15 for Palliative Care; HADS – Hospital and Anxiety Depression Scale; XRT- radiotherapy

Palbociclib (75 or 100 or 125 mg PO daily x 21 days, then 1 week off) and hormone therapy (at standard doses) must have started at least 28 days before radiotherapy is administered. Standard hormone therapy can be tamoxifen, faslodex, or an aromatase inhibitor with or without LHRH agonist.

To participate on this study, patients must fulfill all eligibility criteria and must not meet any exclusion criteria, as well as consent to blood draws and resulting biospecimen collection and analysis.

1.0 OBJECTIVES

1.1 Primary Objective

To evaluate the response rate three months post conventionally fractionated radiotherapy, relative to baseline, for bone metastases in breast cancer patients receiving concurrent palbociclib and hormone therapy treatment

1.2 Secondary objectives

a) To determine whether conventionally fractionated radiotherapy in combination with palbociclib and hormone therapy in breast cancer patients with bone metastases adversely increases the frequency and severity of palbociclib toxicities including Grade 3 neutropenia

b) To determine whether radiotherapy in combination with palbociclib in breast cancer patients with bone metastases adversely increases the frequency and severity of radiotherapy toxicities including neurological and bone injury

c) To assess fatigue, quality of life, and depression before and after radiotherapy for bone metastases in metastatic breast cancer patients treated with palbociclib

d) To determine progression free survival (PFS) and overall survival (OS) in breast cancer patients treated with palbociclib and concurrent radiotherapy to bone metastases

e) To evaluate the relationship between volume of irradiated bone and side effects of treatment, including leukopenia and neutropenia

Translational Research Objectives

a) To collect, store, and analyze ctDNA in metastatic breast cancer patients treated with palbociclib and radiotherapy to bone metastases and to determine the relationship between ctDNA and responders versus non-responders, PFS, and OS

b) To collect, store, and analyze plasma for inflammatory cytokine measurements and determine their relationship with fatigue, depression, and quality of life before and after radiotherapy for bone metastases in metastatic breast cancer patients treated with palbociclib

c) To collect, store, and analyze RNA for gene expression to identify functional biology processes over-represented in genes differentially regulated among patients who develop toxicities versus those who do not and those who are responders versus those who are not and to identify transcriptional regulatory pathways driving observed differences in gene expression.

2.0 Background and Rationale:

Approximately two-thirds of breast cancer patients have tumors that are hormone receptor (i.e. estrogen and/or progesterone receptor) positive. Among hormone receptor positive, her2/neu negative breast cancer patients, as many as 6% will present with metastatic disease at diagnosis, and up to a third will go on to develop metastatic disease after definitive treatment.(1) As metastatic hormone receptor positive breast cancer is a highly prevalent and incurable problem, developing novel therapeutics is imperative. For many years, scientists have become increasingly intrigued by cell cycle inhibition as a strategy for developing novel cancer treatments, and preclinical studies have shown that palbociclib, a highly effective and selective reversible inhibitor of CDK4 and CDK6, is both cytostatic and cytoreductive in hormone receptor positive breast cancer cell lines. These studies also showed that the likelihood of clinically significant drug-drug interactions between palbociclib and all forms of hormone therapy is low.

Subsequently, randomized trials found that palbociclib in combination with hormone therapy (i.e. fulvestrant and letrozole) more than doubled median progression free survival compared with hormone therapy alone in the first or second line setting after progression on endocrine therapy in patients with hormone receptor positive, Her2/neu negative metastatic breast cancer.(2-4) Studies of other cdk 4/6 inhibitors have indicated that additional hormone therapies (i.e. tamoxifen, anastrozole) in combination with a cdk 4/6 inhibitor lead to significant improvements in disease free survival in metastatic breast cancer patients with hormone receptor positive disease.(5) Furthermore, all patients with this disease appear to benefit from this combination of therapies regardless of menopausal status.(3, 5, 6) Although concurrent palbociclib and hormone therapy have led to more patients living longer without disease progression, one of the most common side effects of palbociclib is grade 3-4 neutropenia, impacting approximately two-thirds of women for more than 7 days after the end of a treatment cycle.(3, 4) When neutropenia does occur, it tends to occur early, frequently after the first cycle (each cycle is 28 days, 3 weeks of palbociclib, 1 week off). However, the neutropenia is non-cumulative, reversible, and infectious complications, including febrile neutropenia, are exceedingly rare. (2-4) Fatigue, anemia, and GI distress in the form of diarrhea, constipation or vomiting, and dyspnea are the most common non-hematologic effects of palbociclib. In the Phase II 1003 study, patients treated with palbociclib and letrozole versus (vs.) those who received letrozole alone had significantly higher rates neutropenia (75% vs. 5%, respectively), leukopenia (43% vs. 3%, respectively), fatigue (41% vs. 23%, respectively), anemia (34.9% vs. 6.5%, respectively), nausea (28% vs. 13%, respectively), hot flashes (23% vs. 12%, respectively), alopecia (22% vs. 3%, respectively) and diarrhea (21% vs. 10%, respectively). In PALOMA-1, although 40% of patients required a dose reduction or delay due to palbociclib-related toxicities, these patients still benefitted from the CDK4/6 inhibitor.(6) Given the efficacy and acceptable toxicity profile of palbociclib and hormone therapy, the Federal Drug Administration approved its use in metastatic hormone receptor positive breast cancer patients in 2015. Collectively, these data indicate that there is no evidence that palbociclib and hormone therapy is associated with any clinically significant long-term or cumulative toxicity. The United States Package inserts of both palbociclib and hormone therapy, including letrozole, anastrozole, tamoxifen, fulvestrant, and exemestane provide publicly available and complete information which serve as the Single Reference Safety Documents for these compounds.

Given the improvements in DFS with palbociclib and hormone therapy among metastatic breast cancer patients, clinicians are increasingly challenged by the best way to integrate palliative radiotherapy with palbociclib when patient's progress and/or are symptomatic from their metastases.

Bone is the most common site of metastatic disease among hormone receptor positive, her2/neu negative breast cancer patients. These metastases are often painful and may put patients at risk for fracture and cord compression, particularly if these lesions are located in weight bearing regions or the spine. Radiotherapy is a mainstay treatment for bone metastases, as it has been shown to alleviate pain, stabilize bone, and/or prevent fracture.(7, 8) However, known side effects of radiotherapy include leukopenia, neutropenia, and fatigue, and there is concern that radiotherapy treatment for bone metastases in breast cancer patients concurrently receiving palbociclib and hormone therapy may exacerbate pre-existing neutropenia and fatigue stemming from palbociclib alone. Additionally, murine models have shown that palbociclib may be a radiosensitizing agent (9), potentially increasing the risk of injury to the bone, and other critical structures incidentally treated with palliative radiotherapy (e.g. spinal cord), even with standard radiotherapy doses (30 Gy in 10 fractions or 20 Gy in 5 fractions) known to palliate patient symptoms safely when given in isolation. However, other studies have shown that cdk4/6 inhibition may prevent radiation-induced injury (10) and potentially limit the efficacy of radiotherapy in palliating pain and/or decreasing the high rate of radiographic response (~60%) in treated bone metastases. Alternatively, some physicians are concerned that holding the palbociclib during a five to ten day course of standard palliative radiotherapy is a time during which other metastatic disease may arise or previously responsive, non-osseous disease may recur and progress. Indeed, in vitro data suggests that palbociclib causes cell senescence, and malignant cells will start to repopulate after removing palbociclib and/or hormone therapy after receiving treatment with both medications for a prolonged period. (Lee et al. Abstract no.LB-136. presented at 2014 AACR Annual Meeting, San Diego, CA). To date, only one retrospective study of five metastatic breast cancer patients treated with concurrent conventionally fractionated radiotherapy and palbociclib has been published.(11) These results do not indicate any increase in toxicity or decrease in treatment efficacy compared with radiotherapy and/or palbociclib treatment alone. Furthermore, three of the participating sites on this trial, have continued palbociclib and hormone therapy during palliative radiation in metastatic breast cancer patients since FDA approval of palbociclib. Collectively, they have treated hundreds of metastatic breast cancer patients with this combination of treatments over the last 3 years and have not noticed an increase in toxicity (see attached letters of support). However, these findings need to be confirmed in a prospective setting. The purpose of this study is to evaluate the safety and efficacy of concurrent radiotherapy, palbociclib, and hormone therapy in a Phase II multi-institutional study.

2.1 Rationale for Duration of Palbociclib Treatment prior to Enrollment

Metastatic breast cancer patients who develop grade 3 or 4 neutropenia due to palbociclib and hormone therapy are highly likely to develop this side effect within the first 28 days of treatment. For this proposed study, patients will be required to be on palbociclib for at least 1 cycle (3 weeks of palbociclib and 1 week off) with concomitant hormone therapy followed by a complete blood cell count with differential prior to receiving radiotherapy in order to best distinguish the additional impact radiotherapy may have on leukopenia and neutropenia above and beyond that due to palbociclib and hormone therapy. Given that the majority of metastatic breast cancer patients are initially treated with systemic therapy, this required duration of palbociclib treatment prior to radiotherapy should not preclude a significant number of patients from enrollment.

2.2 Rationale for radiation dose selection:

Two of the most widely used fractionation schemes for palliative radiotherapy in the treatment of bone metastases are 30 Gy in 10 fractions or 20 Gy in 5 fractions. A survey of the radiation oncologists

who staff the seven participating institutions of the proposed study have confirmed the common use of these fractionation schemes in their own practices. Both regimens are considered standard of care with adequate efficacy and low rates of toxicity and have been evaluated in previous randomized trials of palliative radiotherapy. These radiation treatment doses also allow for real time monitoring of radiotherapy side effects over a several day period while a patient is being actively treated. Stereotactic body radiotherapy, high dose radiotherapy (20-35 Gy) given over one to five fractions, is used in a small percentage of metastatic breast cancer patients with oligometastases and typically on trial (i.e. NRG BR002). As the safety of SBRT in breast cancer patients has not been completely evaluated, SBRT will not be allowed in the current study to allow for full evaluation of the efficacy and safety of the most commonly used palliative radiotherapy (30 Gy in 10 fractions or 20 Gy in 5 fractions) in the setting of breast cancer patients with metastatic disease.

2.3 Rationale for Study Endpoints:

2.3.1 Response Rate

Response rate at 3 months post radiotherapy will be the primary endpoint of this study. The majority of enrolled patients will be prescribed radiotherapy for pain symptoms arising from bone metastases, and in these patients, we will use the validated Brief Pain Inventory to assess response. A 2 point score difference in the maximum pain score item on the BPI is considered a clinically meaningful difference, and has been used in other studies of palliative radiotherapy for bone metastases.(7, 12, 13) Among patients who are treated for painful bone metastases, the BPI will serve as the primary measure of response irrespective of imaging findings. In other patients, radiotherapy will be prescribed to stabilize bone, neurological symptoms, or prevent fracture, and in these patients, response will be assessed by imaging. Previous studies of PET/CT, MRI, and bone scan have been used to evaluate breast cancer bone metastases and response to radiotherapy within the bone with some finding an imaging correlate of pain relief.(14-17) In one study, 96% of patients had at least a partial response to radiotherapy on PET/CT with a median time to first post-therapy PET of 1.2 months (range; 0.5-4.1).(16) Although PET/CT is not standard imaging in metastatic breast cancer, similar findings have been seen in CT and bone scan studies, as well as MRI. Using the Brief Pain Inventory or imaging to assess response will allow us to fully explore if the same number of patients who typically respond to radiotherapy alone (~60%) also respond to palbociclib, hormone therapy, and radiotherapy administered concurrently.(7, 17, 18) Admittedly, RECIST criteria (version 1.1) cannot be strictly used to assess bone metastases response without soft tissue component, and there are some studies which have found a high false positive rate of disease progression at three months post radiotherapy.(19) Therefore, among patients who present with pain, responders will be considered those patients who have a 2 point decrease in the maximum pain item on the BPI, and among those who do not present with pain (radiotherapy due to risk of unstable fracture or risk of cord compression), responders will be considered those without development of a pathologic fracture or worsening neurologic compromise (cord compression) due to cancer on imaging.

Response will be defined, therefore, by the following criteria:

- **At least a 2 point decrease** in the Brief pain Inventory item maximum pain score at 3 months post radiotherapy compared with baseline measures among patients with a painful bone metastases to be treated on protocol at the time of enrollment

  -or-

- **No development of outcome for which radiotherapy was administered** (e.g. prevention of new pathologic fracture or new cord compression as appropriate) or **obvious tumor growth within the radiotherapy treated area on imaging** 3 months post radiotherapy among patients who do not have pain in the bone metastases to be treated on protocol at the time of enrollment

Nonresponders will be considered if the following occur:

- **Less than a 2 point decrease** in the Brief Pain Inventory maximum pain item score at 3 months post radiotherapy compared with baseline measures in patients who present with painful bone metastases

  -or-

- **Progression** – Either a new pathologic fracture due to cancer progression or new cord compression symptoms/neurologic compromise among patients who are treated for non-painful bone metastases.

Images will be submitted for central review for possible secondary analysis at the conclusion of the study period.

Secondary assessments of response:

An Update of the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases and personal communication with Dr. Edward Chow, lead author of these guidelines and palliative radiotherapy expert, have recommended using the BPI item rating the *worst pain in the index site over the last 3 days and analgesic intake for pain in the index site in the last 24 hours* to assess response in clinical trials of palliative radiotherapy.(20) A 2 point score difference in the BPI item rating the worst pain at the treated site is considered a clinically meaningful difference and is indicative of at least partial response if there is no increase in pain medication intake; this criteria has been used in other studies of palliative radiotherapy for bone metastases.(7, 12, 13, 20, 21) A complete response to radiotherapy is a BPI maximum pain score of 0 at the index site without increase in analgesic usage.(20) Among patients who are treated for painful bone metastases, the BPI item rating the worst pain in the last 3 days and analgesic intake in the last 24 hours, will serve as a secondary measure of response consistent with the international consensus on palliative radiotherapy endpoints.

In other patients, radiotherapy will be prescribed to stabilize bone, neurological symptoms, or prevent fracture, and patients who do not present with pain at the index site will be considered responders if they do not develop the outcome for which radiotherapy was administered (e.g. prevention of new bone fracture or cord compression) or do not develop obvious tumor growth on imaging, as in the primary measure of response above. Therefore, among patients who present with pain, responders will be considered those patients who fulfill the International Bone Consensus response criteria (see below) using the BPI item rating maximum pain over the last 3 days at the index site and analgesic usage for the treated site within the last 24 hours prior to assessment.(20) Among patients who do not present with pain (radiotherapy due to risk of unstable fracture or cord compression), responders

will be considered those without development of a new pathologic fracture or worsening neurologic compromise (cord compression) due to cancer on imaging.

Secondary measures of response defined, therefore, by the following criteria:

- **Among patients who present with a painful bone metastases [index site(s)] to be treated on protocol,** response 3 months post radiation treatment will be defined by one of the following criteria per International Bone Consensus response categories(20) :
    - BPI item maximum pain Score of 0 at the index site over the last 3 days with no concurrent increase in analgesic intake (daily oral morphine equivalents, OMED) for pain in the index lesion within the last 24 hours compared with baseline measures

      –or-
    - **At least a 2 point decrease in BPI item maximum pain score over the last 3 days** at the treated site without analgesic increase in daily oral morphine equivalent (OMED) within the last 24 hours for pain in the index lesion compared with baseline measures

      -**or-**
    - **A 25% or more reduction in analgesics (OMED) within the last 24 hours for pain in the index lesion without increase in the BPI item maximum pain** score over the last 3 days compared with baseline measures.

  -or-
- **Among patients without pain in the index site to be treated, response will be categorized by the following criteria:**
    - **No development of outcome for which radiotherapy was administered** (e.g. prevention of new pathologic fracture or cord compression, as appropriate) 3 months post radiotherapy

      –or-
    - **No obvious tumor growth within the radiotherapy treated area on imaging** 3 months post radiotherapy

<u>Nonresponders will be considered if the following occur</u>:

- **Increase in BPI item maximum pain score of 2 points or more 3 months post radiation above baseline at the treated site with stable OMED, or an increase in 25% or more in OMED compared with baseline with the BPI item maximum pain score stable or 1 point above baseline.**

  -or-

- **Progression** – Either a new pathologic fracture due to cancer progression or new cord compression symptoms/worsening neurologic compromise among patients who present with a non-painful bone metastases.

Indeterminate Response

- **Less than a 2 point decrease** in the Brief Pain Inventory score at 3 months post radiotherapy at the treated site with less than a 25% reduction in daily OMED for pain at the treated site or more than a 2 point decrease in Brief Pain Inventory Score at the treated site with increase in OMED for the treated site 3 months post radiotherapy compared with baseline measures in patients who present with painful bone metastases

2.3.2 Rationale for Patient Reported Outcome Assessments

Completion of Patient Reported Outcomes instruments is critical for understanding the impact of palbociclib, hormone therapy, and radiotherapy concurrently for bone metastases in breast cancer patients. The primary endpoint of response to treatment will rely completely on the Brief Pain Inventory (BPI, see below) among patients who present with pain stemming from bone metastases to be treated on protocol. However, quality of life (SF-36, EORTC QLQ-BM22, and EORTC QLQ-C15-PAL,), fatigue (MFI-20), and depression (HADS) will also be evaluated as secondary endpoints. The bodily domain of the SF-36 will allow for assessment of patients who present without pain and for side effects from hormone therapy, namely discomfort arising from night sweats, insomnia, vaginal dryness, and arthralgias.(22)

Pain Assessment:

Brief Pain Inventory **Short Form (BPI)** will be used to assess the severity and location of pain, its impact on daily functions, and pain medications before, during, and up to 3 months post radiotherapy (see Figure 1).(13) A clinically meaningful improvement in pain severity is $\geq$ a 2 point decrease in the BPI in metastatic breast cancer patients.(12) The BPI has been used in previous randomized trials of palliative radiotherapy for bone metastases conducted by the RTOG and is endorsed by the National Cancer Institute as an important, valid, reliable, and responsive tool best applied in the research setting to evaluate pain.(7) Since metastatic breast cancer patients can have pain in other areas besides the intended area to be treated on protocol (e.g. diffuse arthralgias, neuropathy, post-mastectomy pain), the question will be modified by adding “pain in and around the bone to be treated on this study with radiotherapy” to make the items more specific as previously done in prior trials.(23) Participants will be specifically asked to attribute their pain to one or more of several factors including the cancer, radiotherapy treatment, aging, hormone therapy, other medical conditions or medications.

Psychosocial Assessments:

Medical Outcomes Study 36-Item Short Form Version 2 (SF-36**)** will also be used to evaluate quality of life. The SF-36 has been validated in a population of healthy women, and it is one of the most commonly used instruments to assess QOL. Our group and others have used the SF-36 in previous studies of breast cancer patients treated with radiation therapy and chemotherapy in patients with and without pain.(24)

European Organization for Research and Treatment of Cancer Metastases Module (EORTC QLQ-BM22) will also be used to evaluate quality of life and pain outcome. The EORTC-QLQ-BM22 is a bone metastases module which supplements the quality of life instrument, EORTC QLQ-C15-PAL (see below). This instrument has been designed and validated specifically in cancer patients with bone metastases and is reliable, applicable across cultures and a sensitive tool to assess pain, functional interference, and psychosocial aspects of quality of life in patients with bone metastases.(25) The EORTC QLQ-BM22 has been used in previous studies of radiotherapy treatment for bone metastases in breast cancer patients.(26, 27) The update of the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases has made a formal recommendation for the use of the EORTC QLQ-BM22 in all trials of palliative radiotherapy along with the EORTC QLQ-C15-PAL.(20)

EORTC Quality of Life Questionnaire Core 15 for Palliative Care (EORTC QLQ-C15-PAL) is a shortened version of the EORTC QLQ-C30, one of the most widely used health-related quality of life questionnaires in oncology for palliative care research. This 15-item questionnaire retains items/scales pertaining to pain, physical function, emotional function, fatigue, global health status/quality of life, nausea/vomiting, appetite, dyspnea, constipation and sleep without reducing measurement precision found with the larger EORTC QLQ-C30 instrument. ***(28)*** The instrument has been validated in multiple cancer patient populations with metastatic disease and has been used in breast cancer patients receiving palliative radiotherapy for bone metastases.(29-31) The update of the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases has made a formal recommendation for the use of the EORTC QLQ-BM22 in all trials of palliative radiotherapy along with the EORTC QLQ-C15-PAL, as the two questionnaires are complementary to one another.(20)

Multidimensional Fatigue Inventory (MFI-20) will be used to evaluate the presence and severity of fatigue among subjects by self-report.(32) The MFI-20 assesses 5 dimensions of fatigue, including general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation.(33, 34) The MFI has been used to quantify fatigue in cancer patients, and a minimal clinically important difference of 10 points has been established.(35)

Hospital Anxiety and Depression Scale (HADS) will be used to evaluate depression and anxiety.(36) HADS has been used in previous studies of metastatic breast cancer patients and is cited by the National Cancer Institute as a commonly used screening tool for depression in oncology patients.(37, 38)

These assessments are a minimal burden to patients and take approximately 30 minutes to complete. At Emory University, ongoing longitudinal studies of patients receiving radiotherapy and using these instruments has established feasibility and over 95% compliance with completing these forms.

2.3.3 Translational Research Endpoints

Rationale for Collection of Blood Samples

Collection of longitudinal blood samples before and up to 3 months post radiotherapy will allow us to determine biomarkers of local response to radiotherapy, disease progression both locally and systemically, as well as side effects of treatment including hematologic toxicities and fatigue.

Blood Collection - Blood samples will be drawn at the same time of day between 8-11 am (to reduce potential circadian effects) under sterile conditions at visits corresponding to the pre-treatment and 3 months post radiation visit noted in the **SCHEMA** above. Whole blood will be collected into EDTA vacutainer and Tempus Blood RNA tubes for plasma separation as well as mRNA, and ctDNA isolation.

A CBC with differentialwill also be performed to assess hemoglobin, platelet count, and the proportion of immune cell types in each sample prior to treatment, last day of treatment, 1 month and 3 months post radiotherapy. A complete metabolic panel will also be performed prior to radiotherapy, 1 month and 3 months post radiotherapy.

Circulating tumor DNA (ctDNA) – Plasma levels of ctDNA will be measured using targeted assays to detect point mutations including mutations in PIK3CA and ESR1, genes associated with hormone therapy resistance.(39, 40) ctDNA has been shown to be a real time biomarker of response to palbociclib and fulvestrant which can be collected from blood, an advantage in this study, as tissue sampling from bone can be technically difficult, risky, and uncomfortable for patients.(41) Plasma can be frozen for future ctDNA extraction, another advantage for this study given the number of proposed enrollment centers. Dr. Aditya Bardia, Assistant Professor Medicine at Harvard Medical School and Attending Physician in Medical Oncology at Massachusetts General Hospital will provide his expertise in ctDNA analyses. Specimens will be shipped to the Circulating Tumor Cell Center at Massachusetts General Hospital where Dr. Bardia will oversee ctDNA processing.

Plasma Analysis of Inflammatory Markers - Plasma concentrations of sTNFR2 and IL-6 will be determined as previously described using sandwich ELISA according to manufacturer's protocol (R & D Systems, Minneapolis, MN). High sensitivity CRP will be measured using a standard turbidimetric assay. These inflammatory markers have been associated with of depression and fatigue in our previous studies of breast cancer patients (42-44), as well as other studies of pain in breast cancer patients.(45, 46) These samples will be shipped to Dr. Andrew Miller's laboratory at Emory University where concentrations of sTNFR2, IL-1ra, and IL-6 will be determined using sandwich ELISA according to manufacturer's protocol (R & D Systems, Minneapolis, MN). Each determination (excluding the soluble cytokine receptors which require less sample) requires 100-150 ul of sample; all samples will be assayed in duplicate. Quality control plasma of both low and high cytokine concentrations will be included with every assay. The mean inter- and intra-assay coefficients of variation for control samples are reliably 10% or less. Dr. Miller is a Professor in the Emory Department of Psychiatry and Behavioral Sciences and has extensive experience conducting these assays and performing studies on the impact of inflammation on the brain and behavior in cancer patients. CRP will be measured in the CLIA certified laboratory of the Emory University Hospital using a standard turbidimetric assay.

Gene Expression - mRNA will be extracted from bloodcollected directly into Tempus™ Blood RNA Tubes. The A_{260}/A_{280} ratio will be used to assess purity, and the RNA will be reverse transcribed using the cDNA Archive kit (Applied Biosystems). RNA concentrations will be determined by Nanodrop fluorometry and sample integrity will be assessed on the Bioanalyzer, which provides an 'RNA Integrity Number' considered a reliable and industry standard for RNA quality and integrity. RNA samples will be shipped to Dr. Felger's laboratory and mRNA expression will be determined using the Roche KAPA Stranded RNA Seq Kits with RiboErase (HMR) (Pleasonton, CA, USA) in the Emory Integrated Genomics Core. This platform interrogates all known exons of >20,000 well-

annotated human genes and can be run on as little as 100 pg of total RNA, or as few as 10 cells. The format allows for transcript variant (splicing) analysis as well as full length transcript data. Synthetic ERCC spike-in controls will be used and hybridized to the array as an internal normalization control for total input RNA. Arrays will be processed using the Expression Console (Affymetrix) software, and gene expression returned as a log signal intensity after normalization. Our previous studies indicate that the top 2 biologic processes represented in gene ontology analysis among depressed and fatigued breast cancer patients are the immune and defense responses, while transcription factor analysis indicates a relationship between the nuclear factor kappa B pathway and fatigue and depression in these patients.(43) Dr. Jennifer Felger, Assistant Professor, Department of Psychiatry and Behavioral Sciences at Emory University, has expertise in gene expression analyses and will provide bioinformatics analyses of these data.

2.4 Benefit-Risk Assessment

Findings from this trial will answer a highly clinically relevant question. Among the seven participating institutions, three continue palbociclib and hormone therapy during radiotherapy for bone metastases while five withhold palbociclib during the 5 to 10 days of radiation treatment. Anecdotally, there have been reports where patients progress elsewhere in the body when palbociclib is withheld during radiation. Given the large number of metastatic breast cancer patients who are currently taking and will receive palbociclib in the future, the results of the proposed study could have a large and far reaching impact on the clinical management of these patients both with bone metastases and other sites of non-osseous disease. For example, if the concurrent treatment of palbociclib, hormone therapy, and radiotherapy is found to be safe and efficacious, an argument could be made to continue this drug regimen when treating liver or lung metastases and potentially disease within the brain with radiotherapy.

Neutropenia is the most frequent and severe side effect of palbociclib, but it is almost always reversible and not associated with infectious complications. Additionally, growth stimulating factors are not typically needed.

The study visits, additional blood tests, and completion of questionnaires are of minimal additional burden. The majority of the study visits occur during standard of care visits (e.g. baseline visit, last day of radiation, 1 month post radiation). The additional visit 3 months post radiation may occur at the same time as a routine visit and assessment with their medical oncologist who would typically see metastatic breast cancer patients at least every 3 months.

2.5 Rationale for Multi-institutional Participation:

To meet accrual goals within a 12 month period the following seven institutions have agreed to participate in this study. All breast cancer physicians within these centers strongly believe this study will answer a highly clinically relevant question and are committed to its success (see attached letters of support). Emory Glenn Family Breast Center at Winship Cancer Institute, Maine Medical Center, Piedmont Cancer, John B. Amos Cancer Center, Northside Hospital Cancer Institute, Georgia Cancer Center at Augusta University, and the Nancy N. and J.C. Lewis Cancer & Research Pavilion have agreed to enroll patients on the proposed study. Emory and Maine Medical are academic centers with physicians who serve approximately 50 and 25 annual, eligible patients at each institution, respectively. At Emory, there have been 272 patients given prescriptions for palbociclib since 2015. Many of these patients will likely progress within the bone during the study time period, and therefore, our pool of

patients to recruit from is likely going to be larger than 50 per year. The remaining cancer centers are community hospitals within the state of Georgia: Piedmont Cancer, John B. Amos Cancer Center, Northside Hospital Cancer Institute, Georgia Cancer Center at Augusta University, and Nancy N. and J.C. Lewis Cancer & Research Pavilion are community hospitals with strong research experience, particularly with radiation therapy oncology group and now NRG Oncology studies, and infrastructure to support such studies (i.e. IROC certification). Each of these community hospitals treat approximately 10-50 eligible patients annually.

Among major metropolitan cities in the United States, Atlanta was recently noted to have one of the largest disparities in breast cancer outcomes among African American and Caucasian women with black women 40% more likely to die of their disease.(47) Emory, Piedmont, and Northside combined account for 70% of the breast cancer care in the city of Atlanta, and more than 40% of patients served by these hospital systems as well as John B. Amos Cancer, Peyton Anderson Cancer Center, and Nancy N. and J.C. Lew Cancer & Research Pavilion, are African American. This study, therefore, has the potential to address disparities in clinical trial participation due to the number of African American patients we serve in Georgia and Emory's track record of successful recruitment of African American breast cancer patients to clinical trials (~45% of all patients on radiotherapy trials, in particular).(24) Although triple negative breast cancer is more prevalent in African American than Caucasian patients, hormone receptor positive breast cancer is still the most prevalent subtype among all women including African American patients and significant disparities are seen in our state regardless of tumor subtype. There are several advantages to including all of these sites:

1) Accrual goals will be met in a short period of time
2) The study results will be generalizable to more patients, as we will accrue patients served at both academic and community practices, and at least 40% of the patients served by all of the institutions in Georgia are African American, while 95% of the patients at Maine Medical Center are Caucasian. Therefore, there will be the opportunity to evaluate how race may impact our results.

2.6 Hypothesis:

We hypothesize that palliative radiotherapy in combination with palbociclib for treatment of bone metastases in hormone receptor positive, Her2 neu negative breast cancer patients will be equally effective to radiotherapy alone in alleviating pain and controlling disease locally (based on historical data) without significant increase in toxicity typically associated with radiotherapy or palbociclib independently.

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, waivers for inclusion and exclusion criteria are not permitted.
For questions concerning eligibility, please contact the study PI, Dr. Mylin Torres.

3.1 Patient Selection Guidelines

a) Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

b) Women of childbearing potential who are sexually active should be willing and able to use medically acceptable forms of contraception during protocol treatment.

3.2 Inclusion Criteria:

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Pathologically confirmed metastatic breast cancer
3.2.2 Known estrogen, progesterone, and Her2 status of either primary tumor or metastasis
3.2.3 Metastatic ER+ or PR+, Her2/neu negative breast cancer patients with imaging confirming bone metastasis within 60 days of radiation simulation
3.2.4 Must be actively receiving palbociclib (125 or 100 or 75 mg PO daily for 3 weeks followed by a week off during 28-day cycles) plus one of the following hormone therapies for at least 28 days:
a) Fulvestrant (500mg IM injection on days 1 and 15 cycle one and then on day one of each subsequent cycle (28 days) -or-
b) Letrozole (2.5 mg PO daily) -or-
c) Anastrozole (1mg PO daily) -or-
d) Exemestane (25mg PO daily) -or-
e) Tamoxifen (20mg PO daily)
3.2.5 Patients must be willing and able to provide written informed consent/assent for the trial
3.2.6 Age $\geq$ 18 years
3.2.7 ECOG Performance Status $\leq$ 2, KPS $\geq$ 60% within 60 days prior to registration
3.2.8 Must have bone disease that is either symptomatic (i.e. pain) or has a lytic or mixed lytic disease that can be assessed by CT, MRI, bone scan or PET/CT within 60 days prior to radiotherapy on this study
3.2.9 Female or male patients allowed
3.2.10 One previous line of chemotherapy in advanced disease is allowed
3.2.11 Appropriate stage for study entry based on the following diagnostic workup:
- History and Physical Examination within 60 days prior to registration
- Clinical grade CT scans of the chest, abdomen, and pelvis with radionuclide bone scan OR whole body PET/CT documenting metastatic disease prior to radiotherapy on this protocol or MRI documenting site of metastatic disease to be treated on protocol

3.2.12 Patient must be eligible for palliative radiotherapy (conventional radiation either 30Gy in 10 fractions or 20 Gy in 5 fractions) for up to 4 separate anatomic regions containing bone metastases defined by 4 separate and not overlapping radiation plans.
3.2.13 CBC with differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follow:
- Absolute neutrophil count $\geq$ 1000/mcl
- Platelets $\geq$ 75,000 mm^3
- Hemoglobin $\geq$ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb $\geq$ 8.0g/dl is acceptable)

3.2.14 For females of child-bearing potential, negative serum or urine pregnancy test within 14 days prior to radiation simulation.
3.2.15. The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.
3.2.16. Prior Treatment:
a) Patients may or may not have received radiotherapy or neoadjuvant or adjuvant chemotherapy in the treatment of their initial, non-metastatic breast cancer, but must be

entered on study after their last dose of radiotherapy, last cycle of chemotherapy and biologic therapy (if applicable) and have sufficient resolution of side effects per physician assessment at time of radiotherapy

b) Patients must have not active wound healing issues from surgery and sufficient resolution of surgical side effects, per physician assessment, at time of radiotherapy

c) If patients have one line of chemotherapy for advanced disease, patients must be entered on study after their last dose of chemotherapy and have sufficient resolution of side effects per physician assessment at time of radiotherapy.

d) Patients must have already initiated palbociclib (3 weeks on, 1 week off) and hormone therapy for at least 28 days prior to radiotherapy.

e) During radiotherapy, no other investigation or commercial agents or therapy for cancer other than palbociclib, bisphosphonates, rank ligand inhibitors, and hormone therapy should be administered.

f) Patients may have received bisphosphonates or rank ligand inhibitors prior to enrollment on study.

3.3 Ineligibility (Exclusion) Criteria:
Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Co-existing or prior invasive non-breast malignancy (except non-melanomatous skin cancer), unless disease free for a minimum of 3 years
3.3.2 Previous radiation dose, date, fraction size, must be reported for prior invasive malignancy..
3.3.3 Previous palliative radiation to the disease to be treated on protocol (including radiopharmaceuticals)
3.3.4 Patients prescribed SBRT for bone metastasis to be treated on this protocol will be excluded
3.3.5 Metastases to be treated on protocol located within 2 cm from a previously irradiated structure:

a) Spinal cord previously irradiated to > 40 Gy (delivered in $\leq$ 3Gy/fraction)
b) Brachial plexus previously irradiated to >50Gy (delivered in $\leq$ 3Gy/fraction)
c) Small intestine, large intestine, or stomach previously irradiated to > 45Gy (delivered in $\leq$ 3Gy/fraction)
d) Brainstem previously irradiated to >50Gy (delivered in $\leq$ 3Gy/fraction)
e) Whole lung previously irradiated with prior V20Gy >35% (delivered in $\leq$ 3Gy/fraction)

3.3.6 Untreated brain metastases or unstable/progressive brain metastases (imaging of treated brain metastases must be performed within 28 days of registration for this protocol to confirm brain metastases stability)
3.3.7 Severe, active co-morbidity such as CHF or unstable angina within last 6 months, transmural myocardial infarction within the last 6 months. Acute bacterial or fungal infection requiring IV antibiotics at time of registration, COPD or other respiratory illness requiring hospitalization at time of registration
3.3.8 Lactating females must cease expression of milk prior to registration.
3.3.9 Temperature above 100.4 degrees Fahrenheit
3.3.10 HIV positive with CD4 count <200 cells/ microliter. HIV positive patients are eligible, provided they are receiving treatment with highly active antiretroviral therapy (HAART) and have a CD4 count > 200 cells/microliter within 28 days prior to registration. HIV testing is not required for eligibility for this protocol. This exclusion criteria is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
3.3.11 Previous chemotherapy or radiotherapy within 2 weeks prior to registration or patients who have not recovered from adverse events due to previous chemotherapy and radiotherapy

3.3.12 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy. Indolent cancers (such as low risk prostate or In-Situ cancers) that are not being treated are acceptable
3.3.13 Has active autoimmune disease that has required continued systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
3.3.14 Has an active infection requiring systemic therapy
3.3.15 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
3.3.16 Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
3.3.17 Cannot receive concurrent cytotoxic chemotherapy (e.g. taxanes, Cytoxan, anthracyclines, platinum based aged, capecitabine) at time of registration or during radiation treatment on this study
3.3.18 Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 90 days after the last dose of trial treatment.
3.3.19 Absolute neutrophil count <1000/mcL
3.3.20 Platelets < 75,000 mm
3.3.21 Hemoglobin < 8.0 g/dl
3.3.22 Concurrent therapy with other Investigational Products is not allowed
3.3.23 Receiving medications or substances that are potent inhibitors or inducers of CYP3A isoenzymes, as palbociclib is primarily metabolized by CYP3A4 enzymes, within 7 days of registration:

- Inhibitors – boceprevir, clarithromycin, indinavir, delavirdine, conivaptan, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, voriconazole, amprenavir, atazanavir, diltiazem, erythromycin, fosamprenavir, verapamil, and grapefruit, grapefruit juice or any product containing grapefruit
- Inducers – carbamazepine, phenytoin, primidone, rifampin, rifapentine, St. John's wort, felbamate, nevirapine, phenobarbital, rifabutin

3.3.24 Receiving hormone replacement therapy (e.g. topical estrogens, but not intra-vaginal preparations, raloxifene, megestrol acetate)
3.3.25 Patients with clinical signs of cord compression. Patients with radiographic evidence of cord compression are eligible for enrollment but cannot have clinical signs of cord compression.

4.0 RESPONSE/FAILURE DEFINITIONS

A responder will be defined as a patient who has one of the following:

a. At least a 2 point decrease in the Brief Pain Inventory item maximum pain score at 3 months post radiotherapy compared with baseline measures in patients who present with pain from bone metastasis to be treated on protocol at the time of enrollment

-or-

b. No development of outcome for which radiotherapy was administered (e.g. prevention of new pathologic fracture or new cord compression, as appropriate) or obvious tumor growth within the radiotherapy treated area on imaging 3 months post radiotherapy among patients who do not have pain in the bone metastases to be treated on protocol at the time of enrollment

Patients who do not fulfill one of the above criteria will be considered a non-responder.

Imaging – Bone metastases must be seen on standard imaging (CT, MRI, Bone Scan, PET/CT) within 60 days prior to radiotherapy simulation. 3 months post radiotherapy (See **Figure 1**), providers must make every effort to use the same imaging method that was used to originally detect the metastases being treated on protocol. Using the Brief Pain Inventory or imaging to assess response will allow us to fully explore if the same approximate number of patients who typically respond to radiotherapy alone (~60%) also respond to palbociclib, hormone therapy, and radiotherapy administered concurrently.(7, 17, 18) RECIST criteria (version 1.1) cannot be strictly used to assess bone metastases response without soft tissue component, and there are some studies which have found a high false positive rate of disease progression at three months post radiotherapy.(19) Therefore, among patients who present with pain, responders will be considered those patients who have a 2 point decrease in the BPI, and among those who do not present with pain, responders will be considered those who do not have obvious growth of cancer or development of pathologic fracture due to cancer on imaging compared with baseline studies. Response will be defined, therefore, by any of the following criteria:

- At least a 2 point decrease in the Brief Pain Inventory item maximum pain score at 3 months post radiotherapy compared with baseline measures in patients who present with pain from bone metastasis to be treated on protocol at the time of enrollment

-or-

- No development of outcome for which radiotherapy was administered (e.g. prevention of new pathologic fracture or new cord compression, as appropriate) or obvious tumor growth within the radiotherapy treated area on imaging 3 months post radiotherapy among patients who do not have pain in the bone metastases to be treated on protocol at the time of enrollment

Nonresponders will be considered if the following occur:

- **Less than a 2 point decrease** in the Brief Pain Inventory item maximum pain score at 3 months post radiotherapy compared with baseline measures in patients who present with painful bone metastases

-or-

- **Progression** – Either a new pathologic fracture due to cancer progression or cord compression symptoms/neurologic compromise patients who are treated for non-painful bone metastases.

Images will be submitted for central review for possible secondary analysis at the conclusion of the study period.

Secondary assessment of response:

An Update of the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases and personal communication with Dr. Edward Chow, lead author of these guidelines and palliative radiotherapy expert, have recommended using the BPI item rating the *worst pain in the index site over the last 3 days and analgesic intake for pain in the index site in the last 24 hours* to assess response in clinical trials of palliative radiotherapy.(20) A planned secondary assessment of response will therefore take these measures into account in accordance with International Consensus Guidelines using the following criteria:

Among patients who present with a painful bone metastases [index site(s)] to be treated on protocol, response 3 months post radiation treatment will be defined by one of the following criteria per International Bone Consensus response categories(20) :

- BPI item maximum pain Score of 0 at the index site over the last 3 days with no concurrent increase in analgesic intake (daily oral morphine equivalents, OMED) for pain in the index lesion within the last 24 hours compared with baseline measures

  –or-

- At least a 2 point decrease in BPI item maximum pain score over the last 3 day**s** at the treated site without analgesic increase in OMED within the last 24 hours for pain in the index lesion compared with baseline measures

  -or-

- A 25% or more reduction in analgesics (OMED) within the last 24 hours for pain in the index lesion without increase in the BPI item maximum pain score over the last 3 days compared with baseline measures.

-or-

Among patients without pain in the index site to be treated, response will be categorized by the following criteria:

- **No development of outcome for which radiotherapy was administered** (e.g. prevention of new pathologic fracture or cord compression, as appropriate) 3 months post radiotherapy

  –or-

- **No obvious tumor growth within the radiotherapy treated area on imaging** 3 months post radiotherapy

Nonresponders will be considered if the following occur:

- **Increase in BPI item maximum pain score of 2 points or more 3 months post radiation above baseline at the treated site with stable OMED, or an increase in 25% or more in OMED compared with baseline with the BPI item maximum pain score stable or 1 point above baseline.**

  -or-

- **Progression** – Either a new pathologic fracture due to cancer progression or new cord compression symptoms/worsening neurologic compromise among patients who present with a non-painful bone metastases.

Indeterminate Response

- **Less than a 2 point decrease** in the Brief Pain Inventory score at 3 months post radiotherapy at the treated site with less than a 25% reduction in daily OMED for pain at the treated site or more than a 2 point decrease in Brief Pain Inventory Score at the treated site with increase in OMED for the treated site 3 months post radiotherapy compared with baseline measures in patients who present with painful bone metastases

4.1 Disease Progression and Subsequent Treatment

The following definitions are used for confirmation of oncologic events:

Local recurrence (i.e. non-responder) – defined as pathologic fracture due to disease recurrence or cord compression/neurological compromise or obvious radiological evidence of disease recurrence within the bone site treated with radiotherapy on this protocol or within the bone treated on this protocol. Radiologists will take care to differentiate treated, sclerotic bone reaction from true progression of disease.

Distant disease progression – defined as radiological evidence of disease progression or recurrence in location (s) other than those treated on this protocol

Progression Free Survival - length of time from start of radiotherapy for the breast cancer bone metastases that a patient lives with the disease but it does not get worse

Overall Survival - length of time from the start of radiotherapy for the breast cancer bone metastases that patients diagnosed with the disease are still alive

Patients who develop disease progression should receive best medical therapy as judged per their treating physician. This may include, but not limited to chemotherapy, hormonal therapy, biologic therapy, radiosurgery, cryotherapy, and radio-frequency ablation (RFA).

5.0 TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Trial Design

This Phase II study is designed to determine the efficacy and safety of administering concurrent palliative conventionally fractionated radiotherapy to bone metastases in hormone receptor positive, Her2/neu negative breast cancer patients who are actively receiving palbociclib and hormone therapy.

5.2 Participant Selection

42 hormone receptor positive, Her2/neu negative biopsy proven metastatic breast cancer patients with bone disease and receiving treatment with palbociclib and hormone therapy will be recruited for this study. Assuming a 20% dropout rate, a minimum of 33 patients will be available for analyses. Patients must have bone lesions that cause symptoms which require palliation or if asymptomatic, are at risk for impending clinical event such as cord compression or pathologic fracture.

NOTE: SBRT is not allowed for the lesion to be treated on this protocol.

5.3 Assessments

Screening Phase is the time between the date a patient provides written informed consent and the patient begins radiotherapy. Data collection and procedures during this time period include patient demographics, eligibility requirements, type of endocrine therapy, concomitant medications, medical history, physical examination/vital signs, imaging results, ECOG performance status assessment, adverse events, serious adverse events, laboratory measurements, pregnancy testing (if applicable), biospecimens (blood samples), and PRO assessments. All narcotic analgesics, including regular and breakthrough medications and doses, route of administration (e.g. PO, IV, transdermal), for pain in the index site(s) should be tracked for the 24 hour period prior to assessment and converted to daily oral morphine equivalent for analgesic scoring. For patients presenting with a painful bone metastasis to be treated on protocol and whose analgesic use is sub-optimal and who require titration or changes in pain medications, a 'run-in' period of 1 week between analgesic dosing adjustment and initiation of radiation is recommended to minimize the risk that analgesic effects will confound the measurement of radiation effects.(20)

Only AEs deemed to be serious and related to protocol mandated and not routinely performed procedures have to be reported during this phase.

TABLE 1. PRE-RADIOTHERAPY TREATMENT ASSESSMENTS

Assessments	Prior to Registration (calendar days)	Prior to Radiation Treatment (calendar days)
History/physical examination, Performance Status		≤ 14 days
MRI or CT Scans of the chest, abdomen, pelvis with radionuclide bone scan OR whole body PET/CT	≤ 60 days	

CBC with differential & ANC, platelets, complete metabolic panel		≤ 14 days
Serum/urine pregnancy test (if applicable)		≤ 14 days
Plasma ctDNA, inflammatory cytokine, and RNA blood collection		≤ 14 days
Patient Reported Outcome Assessments*: • Brief Pain Inventory Short Form (BPI)** • Multidimensional Fatigue Inventory (MFI-20) • European Organization for Research and Treatment of Cancer Metastases Module (EORTC QLQ-BM22) • EORTC Quality of Life Questionnaire Core 15 for Palliative Care (QLQ-C15-PAL) • Medical Outcomes Study 36-Item Short Form Version 2 (SF-36 • Hospital Anxiety and Depression Scale (HADS)		≤ 14 days

***The baseline pre-treatment assessments are essential and should be undertaken as close as possible to the time of first radiation treatment delivery.**

****If more than one anatomic region containing bone metastases is treated, a BPI short form must be completed for each anatomic region treated at each assessment.**

TABLE 2. DURING RADIOTHERAPY TREATMENT ASSESSMENTS

Assessment	Weekly Radiation Treatment Visit per Standard of Care	Last Day of Radiation
Patient Reported Outcome Assessments: • Brief Pain Inventory Short Form (BPI)** • Multidimensional Fatigue Inventory (MFI-20) • European Organization for Research and Treatment of Cancer Metastases Module (EORTC QLQ-BM22) • EORTC Quality of Life Questionnaire Core 15 for Palliative Care (QLQ-C15-PAL) • Medical Outcomes Study 36-Item Short Form Version 2 (SF-36) • Hospital Anxiety and Depression Scale (HADS)		X
Adverse event evaluation	X	X
Physical Examination	X	X
Performance Status	X	X
CBC with differential & ANC		X

****If more than one anatomic region containing bone metastases is treated, a BPI short form must be completed for each anatomic region treated at each assessment.** The acceptable assessment window for "Last Day of Radiation" assessments is +/- 48 hrs for physical examination, performance status, and CBC w/ differential & ANC.

TABLE 3. POST-RADIOTHERAPY TREATMENT FOLLOW-UP ASSESSMENTS

Assessment	Post-Radiation Treatment (months)
Patient Reported Outcome Assessments: • Brief Pain Inventory Short Form (BPI)** • Multidimensional Fatigue Inventory (MFI-20) • European Organization for Research and Treatment of Cancer Metastases Module (EORTC QLQ-BM22)	• 1 month • 3 months

• EORTC Quality of Life Questionnaire Core 15 for Palliative Care (QLQ-C15-PAL) • Medical Outcomes Study 36-Item Short Form Version 2 (SF-36) • Hospital Anxiety and Depression Scale (HADS)	
CBC with differential & ANC, platelets, complete metabolic panel	• 1 month • 3 months
Plasma ctDNA, inflammatory cytokine, and RNA blood collection	• 3 months
MRI or CT Scans of the chest, abdomen, pelvis with radionuclide bone scan or whole body PET/CT*	• 3 months
Adverse event evaluation	• 1 month • 3 months
Physical Examination	• 1 month • 3 months
Performance Status	• 1 month • 3 months

***Note:** We strongly encourage the use of the same imaging performed at baseline. The acceptable assessment window for "1 month" post radiotherapy assessments is within 3 to 7 weeks post last day of radiotherapy treatment. The acceptable window for "3 months" post radiotherapy assessments is within 11 to 16 weeks post last day of radiotherapy treatment.

****If more than one anatomic region containing bone metastases is treated, a BPI short form must be completed for each anatomic region treated at each assessment.**

5.4 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy

Patients receiving more than 1 line of chemotherapy for advanced disease prior to registration are **NOT** eligible. Standard of care systemic therapy should be administered at the discretion of the treating medical oncologist in the event of disease progression. It is recommended that the systemic therapy follow standard guidelines for use of chemotherapy, hormonal therapy, bone protective therapy, and biologic therapy as appropriate for the patient's metastatic breast cancer. While receiving radiotherapy to bone metastases on this protocol, concurrent cytotoxic chemotherapy is not allowed. However, concurrent bisphosphonate and rank ligand inhibitors are allowed.

Palbociclib and Hormone Therapy

Eligible patients are those who have had 1 or more cycles of palbociclib (3 weeks of palbociclib at 75 or 100 or 125mg QD, 1 week off for a total of 28 days) and hormone therapy, immediately prior to initiation of radiotherapy. It is required that radiotherapy will be given concurrently with hormone therapy and at least the second cycle (or higher) of palbociclib. No dose reduction for endocrine therapy is permitted, but dosing interruptions are allowed although treating physicians should make every effort to encourage compliance with prescribed hormone therapy by changing medications or

providing drug holidays if necessary. Endocrine therapy treatment interruptions for up to 2 consecutive weeks within 14 days of initiation radiation and during radiation treatment for endocrine therapy-related toxicities or personal reasons are allowed as per investigator's best medical judgment. However, no more than 2 cumulative weeks off endocrine therapy is recommended while patient is on study. Subjects missing more than 2 cumulative weeks of endocrine therapy during the period mentioned above (within 14 days of initiating radiotherapy and during radiotherapy treatment) will be noted and reasons for discontinuation will be recorded. These patients will be continued to be followed according to post treatment follow up.

While receiving radiotherapy to bone metastases on this protocol, patients must be actively receiving palbociclib (125 or 100 or 75 mg PO daily for 3 weeks followed by a week off during 28-day cycles) plus one of the following hormone therapies:

a) Fulvestrant (500mg IM injection on days 1 and 15 cycle one and then on day one of each subsequent cycle (28 days) -or-
b) Letrozole (2.5 mg PO daily) -or-
c) Anastrozole (1mg PO daily) -or-
d) Exemestane (25mg PO daily) -or-
e) Tamoxifen (20mg PO daily)

Palbociclib and hormone therapy will be prescribed to hormone receptor positive, Her2 negative breast cancer patients participating on this study as standard of care. Patients will be reminded to store palbociclib capsules at room temperature (59-86 degrees Fahrenheit) in their original container. Palbociclib (75mg or 100mg or 125 mg) is taken orally once per day with food for 21 days and then 7 days off to complete a 28 day cycle. Patients self-administer the medication. Missed doses of palbociclib should not be made up even if a dose is vomited. Dose should be skipped and NOT retaken the next day. Patient who inadvertently take 1 extra dose during a day must skip the next day's dose. If patients take more than 2 doses of palbociclib in a day, the treating physician should be notified.
Patients should be instructed to record daily administration of both palbociclib and hormone therapy in a drug diary.

During radiotherapy, no other investigation or commercial agents or therapy for cancer other than palbociclib, bisphosphonates, rank ligand inhibitors, and hormone therapy should be administered. Endocrine therapy will be given at standard treatment doses (see above). Adjuvant endocrine therapy will have started for at least 28 days prior to radiation initiation and will be given concurrently with radiation treatment.

For premenopausal women, tamoxifen or LHRH agonist (monthly injections rather than 3 month depot injections are preferred) in combination with tamoxifen or AI is recommended.

For postmenopausal women, non-steroidal aromatase-inhibitors (anastrozole, letrozole) or steroidal aromatase inhibitors (exemestane) are recommended.

In patients who have received radiologic ablation of the ovaries, an LHRH agonist is still needed if the patient is given an aromatase inhibitor.

Hormone therapy is self-administered. Recommended dosing regimens are stated above. Storage conditions are detailed in the package insert and should be followed.

Missed doses of endocrine therapy should not be made up. If a patient had difficulty tolerating endocrine therapy, the treating provider must make every effort to continue the patient on endocrine therapy, including changing the endocrine agent or using short drug holiday, while continuing treatment with palbociclib. For endocrine therapy on this protocol, one treatment cycle is 28 days for data collection purposes.

5.5 Radiotherapy Treatment

The Radiotherapy Treatment Phase is the time period between and including Day 1 and the last day of radiotherapy. Enrolled patients will take palbociclib and hormone therapy during radiotherapy treatment.

Patients will undergo CT simulation in preparation for radiation planning. Patients can be treated with 2-D, 3-D, intensity modulated radiation therapy (IMRT), and Volumetric Arc Therapy (VMAT). 4-20 MV photon beams or 5-20MeV electron beam may be used. Cobalt-60 and proton radiotherapy are not allowed.

More than 1 osseous site may be included in one radiation treatment field. Up to 4 radiation treatment fields separated by at least 2cm may be treated on protocol.

Dose Fractionation

30 Gy at 3 Gy per fraction or 20 Gy at 4 Gy per fraction given over sequential business days excluding weekends and holidays are allowed on this protocol.

95% of the prescribed dose must cover 95% of the PTV (90% of the prescribed dose to 90% of the PTV is permitted and is considered Variation Acceptable). Dmax should not exceed $\geq$ 115% and is not permitted on this study. Other radiation fractionation schemes and SBRT are not allowed.

All institutions must use heterogeneity correction dose calculation algorithms.

Isocenter Placement – It is best to place isocenter near the center of the target lesion. If there are multiple lesions that cannot be treated in a single field, multiple isocenters should be placed with each centered in a separate target lesion.

Patient Immobilization, Simulation, and Localization

Participating subjects will be positioned in a reproducible, comfortable, and stable pose to allow for both reliable and accurate target position during treatment. The immobilization and pose must be reliable enough to ensure that the GTV does not deviate beyond the confines of the PTV. Ideally, multiple bone metastases treated on this study would be treated in one treatment position. However, more treatment positions can be used at the discretion of the treating radiation oncologist.
CT-based treatment planning is required for all patients.

The CT scan must encompass the target metastases, as well as the following necessary organs at risk (OAR) when included in the radiation field:

- Heart
- Organ
- Lungs
- Kidneys
- Spinal Cord
- Brain
- Brainstem
- Lens
- Brachial plexus

CT scans should have uniform slice thickness of ≤5mm. The use of IV contrast is left to the discretion of the treating radiation oncologist but is not required.

On board imaging (OBI) using KV, MV x-rays, cone beam CT or CT on rails at least once every 5 fractions, per standard of care, is required.

Target Volumes
The treating radiation oncologist will contour the gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV), as well as relevant normal structures within the radiation field (e.g. spinal cord, kidneys, lung, and heart).

Metastasis Location Definition:

When defining the GTV, the simulation CT window should be leveled to bone/soft tissue and the radiation oncologist should use additional diagnostic studies as needed to define the GTV which is the entirety of the metastasis.

The bone where each metastasis to be treated on protocol needs to be identified and annotated in the case reports:

- Spinal metastases will be demarcated spinal if the GTV arises within the vertebral bodies or the vertebral body and pedicle or posterior elements. The CTV will include the entire vertebral body (ies) containing the GTV metastases and PTV will be at least a 5mm expansion on the CTV and could include up to one vertebral body above and below the vertebral body (ies) containing the GTV.

- Non-spinal osseous metastases will be demarcated by the bone from which the target lesion primarily arises. CTV will be at least a 7mm expansion on the GTV, contoured at the discretion of the treating radiation oncologist to expand more generously when clinically indicated (e.g. in the case of a femoral neck metastasis, a radiation oncologist may choose to contour the entire femoral head, neck and inferiorly to below the lesser trochanter as CTV). PTV will be an additional 5mm expansion on the CTV.

Treatment Planning
The radiation field should include all of the GTV, CTV, and PTV with at least 90% of the prescription isodose line covering 90% of the PTV, where the maximum hotspot is 115%. Heterogeneity corrections must be used. Every effort should be made to place hotspots in the target lesion.

Planning priorities
Every attempt should be made to achieve planning goals and OAR criteria without receiving a plan score of Deviation Unacceptable. The following are a list of suggested priorities of planning goals:

a) Do not exceed spinal cord, brachial plexus, sacral plexus or cauda equina dose constraints
b) Meet critical structure constraints (see below)
c) PTV coverage with 95% of PTV covered by the 95% isodose line

90% of the prescribed dose to 90% of the PTV is permitted and is considered Variation Acceptable. Dmax should not exceed $\geq$ 115% and is not permitted on this study. Other radiation fractionation schemes and SBRT are not allowed.

Overlap with prior radiation volumes is not allowed. Radiation fields to be administered on this protocol must be more than 2cm from prior radiation treatment, as the toxicity of palbociclib with radiation is unknown and could be enhanced in areas where radiation has been previously administered.

Critical Structures:

Note: If any of the structures below are within 3cm of any metastases or included in any of the radiation fields to be treated on this protocol, it is required that the included structures are contoured and labeled as listed below for radiation data submission in DICOM format.

Table 4. STRUCTURE CONTOURING GUIDELINES

Standard Name	Description
GTV	GTV • When defining the GTV, the simulation CT window should be leveled to bone/soft tissue and the radiation oncologist should use additional diagnostic studies as needed to define the GTV which is the entirety of the metastasis
CTV	GTV with at least a 7mm expansion, contoured at the discretion of the treating radiation oncologist to expand more generously when clinically indicated, or if spinal metastasis, entire vertebral body (s) containing the GTV should be considered the CTV
PTV	CTV with at least a 5mm expansion, excluding expansion outside of the external contour +

	0.5cm internal to the external contour, and could include up to one vertebral body above and below the vertebral body (ies) containing the GTV when treating vertebral metastasis(es)
External	Body Surface
SpinalCord	Spinal cord • Should be contoured starting at least 10cm above superior extent of PTV and continuing on every consecutive CT slice at least 10cm below inferior extent of PTV but does not extend inferiorly below L2
Heart	Heart • Start contouring at the bifurcation of the pulmonary arteries and continue on every CT slice containing heart and extend inferiorly to the apex of the heart • Include the pericardial sac in the contour
BowelBag	Bowel Bag • The small bowel, cecum, and ascending, transverse and/or sigmoid colon should be contoured in one bowel bag starting 1cm above the superior extent of PTV and continuing on every consecutive CT slice to 1cm below PTV excluding muscle and bones and subtract any overlapping non-gastrointestinal normal structures.
R_Kidney	Right Kidney • Right kidney, excluding renal pelvis/collecting system, should be contoured
L_Kidney	Left Kidney • Left kidney, excluding renal pelvis/collecting system, should be contoured
Kidneys	Total Kidneys • Both right and left kidney, excluding renal pelvis/collecting system, should be contoured in their entirety
R_Lung	Right Lung • Right lung should be contoured on lung windowing on CT
L_Lung	Left Lung • Left lung should be contoured on lung windowing on CT
Lungs	Combined Left and Right Lungs • Both lungs should be contoured as one structure on lung windowing on CT

Esophagus	Esophagus • Use mediastinal windowing on CT to delineate the esophagus to include all layers, lumen, and fatty adventitia • Begin contouring at least 10cm above the superior extent of the PTV and continuing every CT slice to at least 10cm below the inferior extent of the PTV
R_BrachialPlexus	Right Brachial Plexus • Contour the major trunks of the Right brachial plexus using subclavian and axillary vessels as a surrogate for the location of the brachial plexus. • Start contouring proximally at the bifurcation of the brachiocephalic trunk into the Right jugular/subclavian veins (or carotid/subclavian arteries) and contour along the subclavian to the axillary vein ending after the neurovascular structures cross the second rib.
L_BrachialPlexus	Left Brachial Plexus • Contour the major trunks of the Left brachial plexus using subclavian and axillary vessels as a surrogate for the location of the brachial plexus. • Start contouring proximally at the bifurcation of the brachiocephalic trunk into the Left jugular/subclavian veins (or carotid/subclavian arteries) and contour along the subclavian to the axillary vein ending after the neurovascular structures cross the second rib.
BrachalPlexus	Total Brachial Plexus • Contour the major trunks of the brachial plexus using subclavian and axillary vessels as a surrogate for the location of the brachial plexus. • Start contouring proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and contour along the subclavian to the axillary vein ending after the neurovascular structures cross the second rib.
CaudaEquina	Cauda Equina

	• Includes the entire spinal canal starting at L1/L2 where the conus begins and extending into the sacrum and filum
Sacralplexus	Sacral plexus • Extends from L5 to S3 and includes the bilateral nerve roots from the neuroforamina to the coalescing of the nerves at the obturator internus muscle

Critical Organ Dose-Volume Limits

Planning priorities for Organs at Risk:
An unacceptable deviation will be assigned to radiation plans which exceed the absolute limits of the spinal cord, cauda equina, sacral plexus, or brachial plexus (i.e. 115% of the prescribed dose to >0.03cc of any of these OARs).

Every effort will be made to cover 100% of the GTV with 100% of the prescribed dose. Ultimately, at least 90% of the PTV must be covered by at least 90% of the prescribed dose or the plan will be considered deviation unacceptable. Radiation plans will be considered unacceptable if any of the criteria below in the table "**CRITICAL ORGAN DOSES**" are **not** fulfilled.

TABLE 5. CRITICAL ORGAN DOSES

Structure	Volume	Dose/Volume
Spinal Cord	<0.03cc	>115% prescribed total dose
Brachial plexus	<0.03cc	>115% prescribed total dose
Cauda equina	<0.03cc	>115% prescribed total dose
Sacral plexus	<0.03cc	>115% prescribed total dose
BowelBag	<0.03cc	>115% prescribed total dose
Total Lungs	V20	<35%
Esophagus	Mean	<30 Gy
Kidney, bilateral	Mean	<15 Gy
Kidney, bilateral	V12	<55%
Heart	Mean	<20 Gy
Brain, brainstem	<0.03cc	>115% prescribed total dose

Composite Dose Calculations

When more than one radiation field is used to treat multiple metastases, composite plans which include total dose summation from the multiple treatment sites on a single CT scan that encompasses relevant anatomy, must be generated to incorporate dose to surrounding normal tissues. These composite plans must include a planning CT dataset that incorporates all targets and relevant critical structures. When more than one field is used to treat multiple bone metastases, it is advisable to treat all lesions with the patient in the same position. Contact the study PI, Dr. Mylin Torres, if there are technical challenges in summing dose and generating composite plans.

Composite dose plans including all treated metastases and OARs must be submitted. To facilitate composite planning, dose to all metastases should be calculated on a single CT scan. If this is not possible, dose from each separate metastasis treatment plan should be generated and incorporated on the composite plan.

5. Documentation Requirements

Treatment interruptions, including reasons for treatment breaks, must be clearly documented in the treatment record. However, treatment interruptions should be avoided generally.

Sites will record dose-volume values for all required structures on a datasheet which will be submitted with the digital radiation data to Emory University for review.
If re-irradiation of the index lesion is deemed necessary after protocol treatment, it is preferred that re-irradiation be performed 3 months or later after initial radiation and after the last protocol assessment and should only be considered at least 4 weeks after initial treatment on protocol. If re-irradiation of the index lesion occurs, it must be documented.

6.0 BIOSPECIMEN COLLECTION AND SUBMISSION

Tables 1 and 3 summarize the biospecimens that are to be collected from participants at specific study time points. For all participants, biospecimen collection is mandatory, unless otherwise specified and/or specifically prohibited by local regulations or patient refusal. Instructions for collection, on-site processing, storage, and shipping are listed below.

Collection
Blood samples (35 mL total) will be drawn at the same time of day between 8-11 am (to reduce potential circadian effects) on a fasting stomach under sterile conditions at study visits corresponding to the pre-treatment and 3 months post radiation visit noted in **Figure 1. STUDY SCHEMA** above.

TABLE 6. BLOOD COLLECTION TIMEPOINTS

Sample Type	≤ 14 Days Prior to Radiation	3 Months Post Radiation Completion
Plasma for circulating tumor DNA (ctDNA)	X	X
Plasma for cytokines	X	X
RNA Tempus Tube	X	X

6.1 Circulating Tumor DNA

Step #1 - Blood Draw

a) 20ml (or two 10 ml Cell-Free DNA BCT Streck tubes) is collected by any standard phlebotomy technique from a peripheral access point or from a central line by trained personnel.
b) Tubes are inverted about 10 times immediately after collection.
c) Samples are the prepared for transportation to the laboratory for processing (within 24 hours).

Step #2 - Plasma Processing (in Laboratory)

a) Perform this step once for each patient (does not need to be repeated for subsequent blood draws): transfer 1 mL whole blood with a pipette to a pre-labeled 2 mL cryogenic vial, round bottom, self-standing
b) Streck tubes are centrifuged at room temperature for 10 min at 1600 (±150) g.
c) After centrifugation, remove tubes from centrifuge and transfer supernatant of the Streck tubes to one fresh 10 ml polypropylene centrifuge tube without disturbing the cellular layer using a disposable serological pipette or disposable bulb pipette.
d) Centrifuge the plasma in the 10 ml centrifuge tube at room temperature for 10 min at 3000 (±150) g.
e) After centrifugation, remove tubes from centrifuge and transfer supernatant to a fresh 10 ml centrifuge tube without disturbing the cellular layer using a disposable serological pipette or disposable bulb pipette. After transferring the plasma to a new 10 ml centrifuge tube as described, gently mix plasma and record total plasma volume (~8-10 ml plasma per 20 ml blood).
f) Transfer 1 ml plasma aliquots with a pipette to 2 ml pre-labeled cryogenic vials.
g) Place plasma tubes into storage box and freeze plasma in freezer upright in storage box at -80°C or colder. *Short time storage at -20°C is possible.*

Step #3 - Specimen Storage

a) Sample are maintained continuously at -80°C or colder.
b) When outside the freezer, such as when transferring to a different freezer in another location or preparing for shipment, boxes containing tubes should be covered with dry ice.
c) Freezer or dry ice specimen storage container temperature must be checked and monitored Document any deviation from protocol.
d) The freezer or dry ice storage box containing the specimens should either be locked or in a secure area accessible only to authorized study staff.
e) A backup storage plan should be in place in the event of freezer failure.

6.2 Inflammatory Markers and RNA

15 mL is collected for cytokines and RNA analysis from patients under conditions noted above and at the same time as blood collection for ctDNA.

Cytokines/Inflammatory Markers:

1. Collect blood using two purple-top 4mL EDTA vacutainers.
2. Carefully and slowly invert the lavender top tube 3 times
3. Within 1 hour of collection, centrifuge sample under the following settings:
    - 3000rcf, 10 minutes, 4°C, brake on.
4. Gather six (6) 1.5ml microcentrifuge tubes and place on wet ice to cool.
5. Once centrifuged, pipette 500µl of plasma into 6 microcentrifuge tubes.

Buffy Coat Extraction:

6. Using a blunt-tip pipette, collect thin white layer between plasma and red blood cells from each vacutainer, and transfer to two 1.5mL microcentrifuge tubes.
7. Immediately store all plasma and buffy coat tubes at -80°C.

Tempus Tube for RNA:

1. Collect blood using 3mL Tempus Tube
2. After collection, shake thoroughly and vigorously for 10-15 seconds and place on wet ice.
3. Store immediately at 4°C to temporarily cool.
4. Following plasma/buffy coat extraction, store tempus tubes at -20°C in designated freezer box. Vortex or shake well before transferring to freezer.

Label each tube collected above before freezing. Labels should have the following information:

1. Study Name
2. Patient ID
3. Visit (Pre radiotherapy or Post radiotherapy)
4. Sample Type (plasma, RNA)
5. Date
6. Corresponding Barcode (if applicable)

6.3 SHIPPING OF BIOSPECIMENS

Only an authorized shipper can send out biological samples.

6.3.1 Shippers will schedule a pickup beforehand, via FedEx (phone or web):
- 1.1.1. 1-800-GO-FEDEX [1-800-463-3339]
- 1.1.2. FedEx.com

6.3.2 The study sponsor and PI will be responsible for setting up a FedEX account for all participating institutions to use to ship samples.

6.3.3 Arrange shipment on the same day that samples are to be packaged, as to avoid thawing of dry ice. Whenever possible, please store samples locally and then ship in batch, after last specimen collection from last enrolled subject, to Emory University (plasma for inflammatory markers, buffy coat, tempus tubes) or Massachusetts General Hospital (plastma for ctDNA from Streck tubes).

6.3.4 Packaging samples:

Items needed:

6.3.5 Dry Ice

6.3.6 Styrofoam cooler

6.3.7 Cardboard box regulated and designated for shipping

*cooler must fit tightly in cardboard box as to not allow room for movement.

6.3.5 Before preparing shipment, make sure that all packaging is not damaged.

6.3.6 Place cooler in cardboard box and fill cooler about ¼ full with dry ice.

6.3.7 Place sample box (or boxes) in biohazard bag.

6.3.8 Place box in cooler, then proceed to fill cooler with dry ice around the sides and top, if possible.

*DO NOT TIGHTEN COOLER LID, AS THIS CAN CAUSE THE PACKAGING TO EXPLODE.

Label package with appropriate stickers and information:

6.3.9 FedEx Shipping Form

6.3.10 Class 9 Hazard label, for dry ice.

6.3.11 Shipper/Receiver contact information

6.3.12 Dry Ice weight (kg).

6.3.13 UN3373 label – for Biological Substance, category B

6.3.14 Include an itemized list of contents between the secondary container and outer packaging.
6.3.15 Record shipping departures in appropriate log.

7.0 COMPLIANCE CRITERIA

Radiation
Each bone metastases may be treated to a dose of 30 Gy at 3 Gy per fraction or 20 Gy at 4 Gy per fraction on protocol. Treatments should be given on sequential business days, excluding weekends and holidays.

- If a patient receives 30 Gy at 3 Gy per fraction, acceptable variation is treatment completing in >2 but <3 weeks. Unacceptable Deviation is >3 weeks.
- If a patient receives 20 Gy at 4 Gy per fraction, acceptable deviation is treatment completing in >1 but <2 weeks. Unacceptable Deviation is >2 weeks.

PTV goal coverage is at least 95% of the PTV covered by at least 95% of the prescribed dose with dose not exceeding 115% of the prescribed dose.

- Variation **acceptable** is at least 90% of the PTV covered by at least 90% of the prescribed dose
- Deviation unacceptable is <90% of the PTV covered by at least 90% of the prescribed dose or <90% of the dose covering 90% of the PTV.

Palbociclib and Hormone Therapy
To capture adherence to both standard dose regimens of oral palbociclib and hormone therapy, drug diaries will be maintained for all patients. Diaries will be completed by the patient and reviewed for accuracy with the patient at each study visit. Patients who are non-adherent with their medications may receive phone calls and/or extra study visits to encourage adherence. Non-adherence will be documented within the chart and reported to the study PI.

Data from the drug diaries of all enrolled patients will be entered into the electronic data submission forms. For each 28 day cycle, data regarding the number of days palbociclib and/or endocrine therapy were taken as well as number of days palbociclib and/or endocrine therapy should have been taken will be entered. Adherence will be determined by number of days taken divided by number of days drug should have been taken over the time period of the study.

8.0 DISEASE MONITORING

All patients, including those who discontinue protocol therapy early, will be followed for oncological events and death per ASCO guidelines until last study visit.

The following definitions are used for confirmation of oncologic events:

Local recurrence (i.e. non-responder) – defined as radiological evidence of disease recurrence within the bone site treated with radiotherapy on this protocol or pathologic fracture, cord compression/neurological compromise due to disease recurrence within the bone treated on this protocol. Radiologists will take care to differentiate treated, sclerotic bone reaction from true progression of disease.

Distant disease progression – defined as radiological evidence of disease progression or recurrence in location other than those treated on this protocol

Progression Free Survival - length of from start of radiotherapy for the breast cancer bone metastases that a patient lives with the disease but it does not get worse

Overall Survival - length of time from the start of radiotherapy for the breast cancer bone metastases that patients diagnosed with the disease are still alive

9.0 SUPPORTIVE CARE GUIDELINES AND GENERAL CONCOMITANT MEDICATION USE

The following concurrent medications are permitted and should be recorded in the source documents and transferred to the electronic data submission forms:

- Antiemetics
- Antidiarrheal therapy
- Antiallergic measures, such as antihistamines, and corticosteroids
- Bisphosphonates – patients may be on it already or may initiated treatment while on protocol therapy
- Agents used to assist in management of endocrine therapy-induced side effects (NSAIDS, gabapentin, duloxetine, venlafaxine)
- Diabetes management medication including metformin
- Rank Ligand inhibitors
- Pain medications

All supportive therapy will be given during the study period at the discretion of the attending physician(s) to optimize medical care as long as they are within the parameters of the protocol and documented on each site's source documents as concomitant medication:

- Anticonvulsants if indicated
- Anti-emetics may be given prior to each fraction to prevent nausea
- Antidiarrheal as indicated by symptomatic diarrhea
- Analgesic premedication or to avoid general discomfort during simulation and treatment is recommended when appropriate.
- Analgesic medications to decrease pain from the bone metastases
- Medications for neuropathy (e.g. gabapentin)
- Corticosteroids if indicated
- Hematopoietic growth factors should not be used during radiation protocol therapy. G-CSF or pegylated G-CSF may have been given as part of prior chemotherapy as indicated by standard parameters, but ANC must be recovered to entrance values for the protocol without ongoing support.
- Herbal products are at the treating physicians' discretion and should be captured on the concomitant medication forms.
- Nutritional supplementation may be administered per standard indications and should be captured on the concomitant medication forms.

- Highly active antiretroviral therapy (HAART) is permitted for HIV affected individuals
- Medications for gastritis and esophagitis including proton pump inhibitors and magic mouthwash

Systemic Therapy

All hormonal therapy is expected to be continued during radiation. Bone supportive therapy may be continued during radiotherapy. Cytotoxic chemotherapy and everolimus are not permitted during the administration of protocol specific radiation. Cytotoxic chemotherapy must be held for at least 28 days prior to radiation treatment on the protocol. Only **one** prior line of chemotherapy in the advanced stage setting is permitted prior to radiation treatment on this protocol. In the event of disease progression, everolimus or cytotoxic chemotherapy may be initiated or resumed 28 days post radiation in the absence of infection or non-healing wound and will be clearly documented. Surgery is not allowed for 30 days prior to or during radiotherapy but may be permitted after radiotherapy is completed.

Changes in systemic treatment including bisphosphonates and hormonal therapy within 4 weeks prior to delivery of radiotherapy and up to 3 months post radiotherapy treatment on protocol should be recorded. Surgery or cytotoxic chemotherapy treatment after completion of radiotherapy on protocol should also be recorded.

Prohibited Concomitant Medications include:

- CYP3A Inhibitors/Inducers (see exclusion criteria)
- Anticancer therapies such as chemotherapy, immunotherapy, targeted therapy, etc. other than allowed on protocol during active treatment.
- Hormone replacement therapy (see exclusion criteria)

Medications not recommended:

- Herbal medicine is not recommended during the treatment phase
- Chronic immunosuppressive therapies should be avoided

Duration of Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), as described in Section 11 below
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

10.0 TREATMENT MODIFICATIONS/MANAGEMENT

Expected toxicities and potential risks of both palbociclib and hormone therapy can be found in the package inserts (see Appendix).

10.1 Palbociclib Dose Modification and Toxicity Management

Dose or treatment modification for palbociclib are allowable and may occur as dose interruptions (within a cycle), dose delays (between cycles) or dose reductions. In general, cycles should be 28 days long unless the start of a new cycle is delayed. If doses are missed within a cycle and the AE resolves before the end of the cycle, then the patient can resume taking the palbociclib for the remainder of the cycle but should still stop on Day 21 to maintain the 7-day break. The start of a new cycles should be delayed according to guidelines below if the AE requiring a dose hold has not resolved by Day of the next planned cycle.

- Palbociclib dose may need to be reduced from 125mg to 100mg or to 75mg, following a cycle delay or dose interruption
- Investigators should manage their patients according to medical judgement and no specific dose adjustments are recommended for Grade 1 or short lasting Grade 2 (<4 weeks) treatment-related toxicity.
- Palbociclib dose reduction from 125mg to 100mg or to 75mg is recommended for all subsequent cycles when the patient develops Grade 2 toxicity lasting >4 weeks (excluding alopecia) or for palbociclib related Grade 3 toxicities despite maximum supportive care. Taking palbociclib with food should be confirmed and reinforced. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. If a patient is taking 75 mg daily of palbociclib, the subjects will still be eligible for enrollment. Dose re-escalation of palbociclib from 75 to 100 mg or 100 to 125 mg is not allowed. If the dose reduction occurs after radiation, this will be noted in the chart and the patient will be assessed at all post radiation study time points per study guidelines.

Palbociclib treatment may be interrupted/delayed until criteria for retreatment are met:

- Uncomplicated Grade 3 or 4 neutropenia resolves so that the ANC >1000/mcL
- Grade 3 or 4 neutropenia with documented infection or fever $\geq$ 100.4 degrees Fahrenheit resolves
- Grade $\geq$3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment) resolves
- All the following parameters are met – platelet count $\geq$75,000/mcl, ANC$\geq$1000/mcl and no fever and any persistent grade $\geq$2 treatment-related non-hematologic AEs considered related to palbociclib have recovered to Grade $\leq$1 or baseline.

CBC with differential including absolute neutrophil count must be done by Day 3 of each cycle of palbociclib. Whenever retreatment after dose delay occurs, the first palbociclib dose day would count as Day 1 of the cycle. If the treatment delay is due to hematologic parameters, the frequency of blood count assessment should be adjusted as clinically indicated. If retreatment parameters are met within 4 weeks of treatment interruption or cycle delay, palbociclib may be resumed.

Palbociclib treatment may be interrupted/delayed if Grade 2 non-hematologic toxicity persists despite optimal medical treatment, lasting more than 3 weeks, and unacceptable to patient and/or provider.

Palbociclib treatment will be permanently discontinued if >3x upper limit of normal ALT and 2x upper limit of normal Total Bilirubin, at any time during the trial.

Patients should not hold or discontinue palbociclib for side effect potentially or likely related to endocrine therapy, as per the physician's judgement.

10.2 Endocrine Therapy Dose Modification and Toxicity Management

No dose reduction for endocrine therapy is permitted, but dosing interruptions are allowed. However, endocrine therapy treatment interruptions for up to 2 consecutive weeks within 14 days of initiation radiation and during radiation treatment for endocrine therapy-related toxicities or personal reasons are allowed as per investigator's best medical judgement. However, no more than 2 cumulative weeks off endocrine therapy is recommended while patient is on study. Subjects missing more than 2 cumulative weeks of endocrine therapy during the period mentioned above (within 14 days of initiating radiotherapy and during radiotherapy treatment) will be noted and reasons for discontinuation will be recorded. These patients will be continued to be followed according to post treatment follow up.

Providers are allowed to change the approved endocrine therapy agents to improve patient adherence (e.g. tamoxifen to AI or vice versa). If a patient has difficulty tolerating a specific endocrine therapy, the provider should make every effort to continue the patient on endocrine therapy by using short drug holidays or changing the prescribed endocrine agent while continuing palbociclib. Patients who discontinue palbociclib, endocrine therapy, or radiotherapy will continue to be followed according to post treatment follow up.

10.3 Radiation Therapy Dose Modification and Toxicity Management

Each bone metastases may be treated to a dose of 30 Gy at 3 Gy per fraction or 20 Gy at 4 Gy per fraction on protocol. Treatments should be given on sequential business days, excluding weekends and holidays. No dose reduction in radiation is permitted, but dose interruptions are allowed. Radiation treatment breaks for up to 2 consecutive business days for radiotherapy-related toxicities or personal reasons are allowed as per the investigator's best medical judgement. However, no more than 2 missed consecutive doses of radiotherapy (weekends and holidays excluded) is recommended per radiotherapy treatment course.

The **Supportive Care Guidelines and General Concomitant Medication** section 9.0 above lists permissible medications for management of toxicities from radiotherapy, endocrine therapy, and palbociclib.

11.0 ADVERSE EVENTS

All treatment related AEs will be scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

(https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

Adverse events related to treatment on this protocol are dependent on the location of the metastases treated as well as OARs included in the radiation field. Fatigue may occur but should be transient

from the radiation. Neutropenia is likely to occur from the palbociclib treatment but this will be monitored for exacerbation during and after radiation treatment with complete blood cell counts and differentials, including the absolute neutrophil count.

11.1 REPORTING ADVERSE EVENTS (AEs)/ SERIOUS ADVERSE EVENTS (SAEs)

All treatment-emergent AEs (events occurring during and up to 3 months post radiotherapy) will be recorded. For participating subsites, adverse events collected at weekly radiation treatment visits are to be entered into OnCore no later than 14 calendar days after data collection. Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according institutional policy. Site investigators must report all serious adverse events (SAEs) and unanticipated problems to the sponsor-investigator within 24 hours of the participating site becoming aware of the event. The participating site will submit the Serious Adverse Event Report Form to the Winship regulatory staff and will also enter the data into OnCore within the specified timelines above. The Emory sponsor must review and sign off on the event and return to the Winship regulatory staff. Regulatory will review the assessment to determine IRB reporting requirements. Subsites are not permitted to report directly to the coordinating center IRB. All external site SAEs are to be reported to the coordinating center multi-site regulatory specialist. The coordinating center multi-site coordinator will facilitate submission of external site SAEs to the coordinating center IRB. All SAEs and other adverse events must be recorded on Serious Adverse Event Report Forms. In addition, all SAEs must be reported to the coordinating center principal investigator and coordinating center multi-site regulatory specialist within 24 hours of knowledge of the event using the Serious Adverse Event Report Form.Copies of de-identified source documentation pertaining to the SAE must be submitted to the coordinating center.

If a patient is permanently withdrawn from the study because of an SAE, this information must be included in the initial or follow-up form. All SAEs must be submitted to the local IRB per local IRB and institutional policy. Upon request of additional data or information that is deemed necessary must be reported to the coordinating center as soon as possible but no later than 5 calendar days.

11.2 Definition of an adverse event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug or radiation related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probably, or definite). (International Conference on Harmonisation (ICH), E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

For example, radiation-related acute toxicities should be recorded in addition to surgical intervention at the treated site, pathological fracture, spinal cord compression, and re-irradiation of the treated site after completion of radiation treatment on protocol.

Pregnancy of a study participant must be reported to the sponsor-investigator in an expedited manner, due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents.

11.3 Assessment of causality of adverse events

Investigators should use their knowledge of the patient, the circumstances surrounding the adverse event, and an evaluation of potential alternative causes to determine whether or not an adverse event is considered to be related to radiation, palbociclib, and endocrine therapy. The following guidelines should be used:

- Temporal relationship of event and treatment with radiotherapy
- Course of the event, considering dose reduction, discontinuation, or re-introduction of palbociclib, hormone therapy, or radiotherapy
- Known side effects of palbociclib, hormone therapy, and radiotherapy
- Natural history of hormone receptor positive, Her2-neu/negative metastatic breast cancer
- Presence of concomitant medications or concomitant illnesses
- Presence of non-treatment-related factors known to be associated with occurrence of the event

11.4 Radiation Adverse Events

Lung Injury
Pneumonitis due to radiation may occur weeks to months after treatment and is caused by inflammation of the end bronchioles and alveoli. Radiation oncologists will be expected to participate in the care and monitoring of enrolled patients for this symptom per standard of care. Patients reporting fever, shortness of breath, dry cough, and/or chest pain should be immediately evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. For severe cases, systemic steroids, bronchodilators, and pulmonary hygiene may be prescribed. Concurrent infections should be treated with antibiotics. Radiation fibrosis is a late manifestation of radiation lung injury.

Gastrointestinal/Esophageal Injury
Radiation may cause esophagitis or dysphagia which typically resolves within a few weeks of radiation. It may also cause permanent injury, although infrequent at the proposed radiation treatment doses, which manifests as dysphagia with stenosis or esophageal ulceration with perforation in the extreme cases. Any of these toxicities must be clearly documented.

Cardiac and pericardial Injury
Although uncommon at the proposed radiation doses on this protocol, radiation treatment to the heart has been associated with pericarditis, endocarditis, coronary artery disease, hypertension, myocardial infarction, and heart failure.

Kidney Injury
Radiation may cause kidney injury but not typically at the doses prescribed on this protocol.

Spinal injury

Radiation can cause myelitis which manifests as paresthesia, sensory changes, and motor weakness including paralysis. Because there is no effective treatment for myelitis, it is critical to prevent and avoid injury to the spinal cord. Corticosteroids may help with symptoms.

Osseous injury
Pathologic fractures and vertebral body compression fractures are extremely uncommon (<8%) at the proposed radiation doses of this protocol. Fractures of bones treated on this protocol will be reported immediately to the study monitor and study PI, Dr. Mylin Torres.

Alopecia, erythema, desquamation are common side effects from radiation for osseous metastasis. Edema, pain, and neuralgia may be additional side effects of the treatment.

11.5 Palbociclib and Hormone Therapy Adverse Events

Palbociclib and hormone therapy are both approved for metastatic disease in the United States. Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of palbociclib and/or hormone therapy may need to be adjusted. Neutropenia, leukopenia, fatigue, anemia, nausea, hot flashes, alopecia, and diarrhea are common side effects of palbociclib. Arthralgias, vaginal dryness, hot flashes, and mood swings, are common side effects of aromatase inhibitors. Hot flashes, mood swings, vaginal changes, and blood clot are possible side effects of tamoxifen.

11.6 Adverse Event Reporting Exceptions

Recurrence or progression of the underlying malignancy is reportable only if the patient dies due to recurrence or progression within the study period. Hospitalization solely due to recurrence or progression of malignancy should not be reported as an SAE. Clinical symptoms of recurrence or progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the recurrence or progression of the underlying malignancy or does not fit the expected pattern of recurrence or progression for the disease under study. If there is any uncertainty about an AE being due to the disease under study, it should be reported as an AE or SAE as appropriate.

12.0 REGISTRATION, STUDY ENTRY, DATA COLLECTION AND WITHDRAWAL PROCEDURES

12.1 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the Winship Regulatory Office before they can be approved to enroll patients. Assignment of site registration status assures that there is a valid IRB approval, and compliance with all protocol specific requirements.

A. Registration and Eligibility

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as ‘approved’. Patients must have signed and dated all applicable consents and authorization forms within 30 days of starting radiotherapy on this protocol.

After each subject signs consent, the Central Subject Registration form is to be completed and sent to Winship within 24 hours of consent. This form, along with the valid, signed informed consent form/HIPAA authorization form, is to be faxed or emailed to Winship’s

Central Subject Registrar per instructions on the form. Once a subject is registered, each participating site will be notified via e-mail.

The Eligibility checklist is to be printed from OnCore and verified by 2 people, of which one must be a clinical investigator or co-investigator. The completed and signed eligibility checklist along with all redacted supporting source documentation must be submitted to the Winship Multi-site Coordinator (MSC) or designee (fax 404-778-0417) within 14 days after pre-registration but no later than 2 business days prior to scheduled treatment visit. Eligibility will be confirmed by the site investigator or co-investigator and the MSC or designee within 1 business day of receipt of all eligibility documentation and confirmation will be sent to the participating site along with a unique patient number or identifier which will remain the same throughout the entire study, if subject meets criteria.

Please contact sponsor principal investigator if there are any questions.

B. Data Collection/Management/Electronic Data Capture

The trained investigator site staff will enter the data required by the protocol into the electronic forms from source documents (e.g. medical records and study specific data capture forms as needed). All information on these electronic forms must be traceable to these source documents. Electronic data forms will be completed for all subjects. For subjects who do not initiate radiotherapy or do not complete radiotherapy, electronic forms will be completed with all data collected up to and at the time of subject study discontinuation.

Automatic validation programs or manual checks for data discrepancies in the electronic data submission form may result in queries for resolution by the investigational site. Designated investigator site staff is required to respond to these queries and make any necessary changes to the data. Winship Cancer Institute and the Study PI will perform audits quarterly for quality assurance of the database.

The clinical management system being used for this study is The Online Collaborative Research Environment (OnCore). OnCore will be used to record all study related information for all registered subjects, including their assigned patient ID and radiation treatment dose. All data must be entered no later than 30 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The MSC will provide OnCore training to each and request access to the appropriate staff at the participating site.

<u>Medical History and Demographic Data</u>

Medical History includes clinically significant diseases that are currently active or that were active, including major surgeries, within the previous 5 years, any cancer history (including prior cancer therapies and procedures) and reproductive status.

Patients are considered postmenopausal if any of the following are true:

- Age ≥ 60 years -or-
- Age < 60 years with intact uterus and amenorrhoeic for ≥ 12 consecutive months prior to chemotherapy and/or endocrine therapy exposure -or-
- Prior bilateral oophorectomy -or-
- Age <60 years with prior hysterectomy and FSH and plasma estradiol levels in the postmenopausal range according to local policies prior to chemotherapy and/or hormone therapy

All other patients who do not fulfill any of the above criteria are considered premenopausal. If there is any question regarding a patient's menopausal status, the physician's judgement needs to be documented in the patient's note and electronic data submitted for the study.

Previous type of neoadjuvant and/or adjuvant therapy (i.e. chemotherapy, radiation, surgery, hormone therapy, targeted therapy, etc.) including start date and end date must be recording in the electronic data submission form by the investigator or delegate at the participating site.

Demographic data will include age, sex, and self-reported race/ethnicity.

Concomitant Medications

Any concomitant medications and treatment will be recorded from 30 days prior to radiotherapy treatment and up to the last study assessment (3 months post radiotherapy completion) whether they are breast or non-breast cancer related therapies.

Physical Examination and Vital Signs

Prior to radiotherapy treatment, a physical examination including assessment of tenderness to palpation over the bone metastases and neurological examination (if applicable), height, weight, blood pressure, and pulse rate is required.
Symptom-directed and treatment directed physical examinations, blood pressure, weight, and pulse rate will be performed at subsequent visits.
All physical exams and vital signs assessments should be performed by a physician or registered nurse or other qualified health care provider according to local regulations.

Laboratory Assessments

It is highly recommended that laboratory assessments be performed at the research center, but if this is not feasible, laboratory tests for individual patients should be performed at the same lab. The frequency of blood draws is detailed in the assessment schedule above.

All initial laboratory assessments must be performed within 14 days of radiotherapy treatment.

- Hgb, white blood cell count (WBC), absolute neutrophil and platelet count
- Serum/urine pregnancy test if required

Additional hematology/chemistry panels (e.g. liver function tests) may be performed as clinically indicated.

Serum or urine pregnancy test must be negative in women judge premenopausal within 14 days of radiotherapy or in women with amenorrhea of less than 12 consecutive months at time of registration. Pregnancy testing does not need to be done in patients who are postmenopausal.

Radiation Dose

The prescribed radiation dose, number of fractions, anatomic site(s) to be treated with radiation, reason for treatment (e.g. pain) will be recorded and collected.

Treatment Compliance

Adherence to both the prescribed radiotherapy treatment regimen as well as palbociclib and hormone therapy will be recorded and collected (please see Compliance above). Protocol deviations from the approved protocol will be documented and explained. The investigator will promptly report any deviations that might impact patient safety and data integrity to the Sponsor and if locally applicable, to the local IRB in accordance with local policies.

Patient Reported Outcome Measures

To fully evaluate the impact of radiotherapy on metastatic breast cancer patients receiving palbociclib and hormone therapy, a comprehensive benefit and risk assessment that includes the patient perspective, in addition to efficacy and safety, will be performed. The BPI, MFI, SF-36, EORT QLQ-BM22, EORTC QLQ-C15-PAL, and HADS will be used to assess pain, fatigue, quality of life and depression, respectively (see **Background and Rationale**). The questionnaires take approximately 30 minutes to complete and will be collected at baseline (prior to radiation), last day of radiation, and 1 and 3 months post radiation time points.

Digital Imaging and Radiotherapy Data Submission

Both patient imaging and radiotherapy data from participating institutions will be exported from the institution's diagnostic imaging department and radiation treatment planning system in DICOM format, and subsequently anonymized using the Velocity Anonymize software from Varian Medical Systems, a software that anonymize images, contours, plan and dose data without compromising the essential links between these radiotherapy objects and thus preserving their ability to be imported in a different treatment planning system at another institution. This vendor-neutral data on patients analyzed in this proposal will be collected on a dedicated research server already available at Emory. Research coordinators or assistants are able to submit standard of care imaging through the same method. (See appendix for detailed instructions)

For patient images stored on a PACS system at the participating institution or site, these images can be sent to Velocity in DICOM format where a research database will be used that does not contain any PHI, only the subject identifier number. Images from the clinical database will be saved to a directory, anonymized using a commercial anonymizer available in the Emory Department of Radiation Oncology (Velocity Anonymize, Varian Medical Solutions), and then uploaded in the research system. The anonymization procedure takes about 10 minutes to complete.

The research server is ideally suited for such projects as it replicates the clinical software environment but has its own database holding project-specific datasets. In addition, the research station has installed the Eclipse Advanced Scripting Programming Language (ESAPI) where researchers can write code in C# to create customized software scripts to extract and analyze patient data according to a project's design. For analysis, we will re-use a script created in the frame of previous research to automatically output plan quality measures to an Excel file for statistical processing. Extracted measures are plan indices such as the conformity, homogeneity and gradient indexes, dose statistics inside targets and critical structures, complete dose-volume histogram graphs, standard constraints values as well as any user-defined DVH points in any either absolute or relative formats for the dose or volume. With an extended version of the script, we can extract radiomics measures such as image features, statistics, and textures. These radiomics features can be extracted from either the patient's CT dataset or the plan's dose distribution. Extracted features also include segmentation characteristics such as the volume, area and tortuosity of each structure in the plan. Once imported in the research database, data received from the participating institutions will be processed with scripts to generate measures for statistical analysis.

If there are any questions regarding this process, please contact Edi Schreibmann, eschre2@emory.edu, 404-778-5667.

C. Monitoring Plan

At the time of study initiation at a non-Emory site, the Emory Sponsor, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings, which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spreadsheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the Emory PI via e-mail.

Winship's multi-site coordinator will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (once annually onsite and three times remotely) until subject follow-up is terminated. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies.

At least monthly teleconferences between Emory PI and participating site.

Teleconferences will be conducted at least once monthly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The PI at Emory will communicate with participating sites via monthly email. The minutes from the teleconference will be maintained in the regulatory binder for

the study. In addition, electronic copies will be sent via email to the principal investigators at each site.

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility. All participating sites on this protocol are IROC certified.

12.2 Multi-Site Monitoring Guidelines

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute at Emory University will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed.Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.
The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

13. DRUG INFORMATION

Please see Background and Rationale, Treatment Planning/Regimen Description, Treatment Modifications/Management, and Adverse Events Sections above for information regarding palbociclib and hormone therapy. The United States Package inserts of both palbociclib and hormone therapy, including letrozole, anastrozole, tamoxifen, fulvestrant, and exemestane provide publicly available

and complete information which serve as the Single Reference Safety Documents for these compounds (See Appendix).

14. SPECIAL STUDIES: None

15. MODALITY REVIEWS

The Study PI will perform a radiotherapy Quality Assurance Review after complete data for the first 10 cases enrolled has been received at Emory. These reviews will be on going.

16.0 STATISTICAL CONSIDERATIONS

16.1 Study Endpoints

Primary Endpoint - Response rate at 3 months post radiotherapy, relative to baseline, defined according to criteria stated above (BPI or imaging).

Secondary Endpoints:

a. Response rate at 3 months post radiotherapy relative to baseline incorporating BPI and analgesic measures according to International Consensus Guideline Criteria(20)
b. PFS
c. OS
d. Adverse Events scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5
e. Fatigue, as measured by MFI before and after radiotherapy, actual scores and change from baseline
f. Quality of Life, as measured by SF-36, EORTC QLQ-BM22, and EORTC QLQ-C15-PAL, actual scores and change from baseline
g. Depression, as measured by HADS, actual scores and change from baseline
h. Adherence, measured by drug diary, and radiation treatment compliance with prescribed radiation dose and days of treatment

16.2 Statistical Methods

Sample size considerations:
Sample size is determined using a non-inferiority study design. We achieve 80% power with a sample size of 33 to detect a non-inferiority proportion of 60% using a one-sided binomial test for non-inferiority and assuming a Type I error of 0.05. This assumes that the current response rate, using the BPI, is 80%. These assumptions are consistent with previous randomized trials of palliative radiotherapy for bone metastases.(7) Assuming an attrition rate of 20%, we will enroll 42 patients.

Accrual will take place at 7 different institutions (see appendix with letters of support). Each hospital system sees between 10 and 50 eligible patients annually, and accrual is expected to reach a rate of 4 patients per month with our last patient enrolled during the last quarter of Year 1. Primary endpoint completion should take place during the first quarter of Year 2.

Primary Endpoint
Response will be estimated as the number of responders divided by the number of patients evaluated for response. A 95% confidence interval for the response rate will be reported using the Clopper-Pearson method.(48) Response rates and confidence intervals will also be reported for subgroups, stratified by bisphosphonate or rank ligand inhibitor use, prior chemotherapy for advanced disease, and number of treated radiation fields.

Secondary Endpoints
Based on an Update of the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases, a planned secondary analysis of response incorporating both the BPI and analgesic measures will also be performed. Adverse events, such as bone fracture following radiotherapy, any Grade 3 toxicity (except neutropenia or leukopenia) including gastrointestinal toxicities, Grade 4 neutropenia, Grade 4 leukopenia, Grade 3 febrile neutropenia, or Grade 3 brachial plexopathy or spinal cord injury, will be summarized descriptively, using frequencies and percentages. Fatigue as measured by MFI will be summarized descriptively both before and after radiotherapy. Pre- and post-radiation MFI scores will be compared using paired t-tests or Wilcoxon signed-rank tests, where appropriate. Quality of Life as measured by SF-36, EORTC QLQ-BM22, and EORTC QLQ-C15-PAL, will be summarized descriptively. Progression-free survival is defined as time from registration to death or progression and will be estimated using the Kaplan-Meier method. Overall survival is defined as time from registration to death and will be estimated using the Kaplan-Meier method. Stratification factors such as bisphosphonate or rank ligand inhibitor use, prior chemotherapy for advanced disease, and number of treated radiation fields will be evaluated across presence of adverse events using chi-squared tests or Fisher's exacts tests for categorical variables, and t-tests or Mann Whitney U tests for continuous variables where appropriate. Univariate and multivariable logistic regression models will be considered for these factors, modeling the presence of adverse events. Stratification factors also will be evaluated across survival endpoints using log-rank tests. Univariate and multivariable Cox proportional hazards models will be considered, and model assumptions will be checked and verified.

Correlative research:
Biomarkers such as cytokines and circulating tumor DNA (ctDNA) will be collected at baseline and 3 months post radiotherapy and will be summarized descriptively at each time point. Mixed models with random intercepts will also be considered, in order to evaluate the biomarkers longitudinally. Biomarker value at baseline and 3 months post radiotherapy, as well as change in biomarker value will be analyzed across response using t-tests or Mann Whitney U tests, where appropriate. Stratification factors such as bisphosphonate or rank ligand inhibitor use, prior chemotherapy for advanced disease, and number of treated radiation fields will be included as fixed effects in the longitudinal biomarker models.

Analysis Datasets:
All eligible patients who receive at least one dose of protocol therapy will be included in the primary efficacy analysis. Safety analysis will be conducted using the Safety Population, defined as any participant receiving at least one dose of study treatment.

16.3 Interim analyses

Stopping rules for toxicity: After 10 patients have been enrolled, we will stop the study if any of the following rates of toxicities are exceeded:

1) >85% of patients develop grade 3 neutropenia
2) >25% of patients develop grade 4 neutropenia
3) >10% of patient develop grade 4 leukopenia
4) >10% of patients develop grade 3 febrile neutropenia
5) >10% of patients develop bone fracture following radiotherapy
6) >5% of patients develop Grade 3 brachial plexopathy (assessed by LENT/SOMA or RTOG criteria) or Grade 3 spinal cord injury assessed by CTCAE version 5
7) >15% of patients develop other Grade 3 toxicities (excluding neutropenia and leukopenia) not mentioned above

17.0 GENDER/RACE/ETHNICITY DISTRIBUTION

Women and men of all race and ethnic groups are eligible for this study. In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, possible interactions between race/ethnicity and treatment have been considered. Based on the racial make-up of breast cancer patients in Georgia (at least 40% African American), and Emory's previous success in enrolling African American patients to breast cancer trials (~45% of subjects are African American), treatment, efficacy, and safety comparisons may be explored among Caucasian and African American metastatic breast cancer patients.

TABLE 7. PROJECTED GENDER/RACE/ETHNICITY DISTRIBUTION OF ENROLLED PATIENTS

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	0	1
Not Hispanic or Latino	40	1	41
Total	41	1	42
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Black or African American	17	0	17
Native Hawaiian or other Pacific Islander	0	0	0
White	23	1	24
Total	41	1	42

18. STUDY TIMELINE

TABLE 8. STUDY TIMELINE

Milestone	Site	GOALS											
		Year 1				Year 2				Year 3			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Participant Accrual*	Emory Glenn Family Breast Center Atlanta, GA	**2**	**3**	**1**	**2**	**1**	**2**	**1**	**2**	**4**	**4**	**4**	**2**
	Piedmont Cancer Institute Atlanta, GA	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
	Georgia Cancer Center at Augusta University	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**
	John B. Amos Cancer Center Columbus, GA	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	The Nancy N. and J.C. Lewis Cancer & Research Pavilion St. Joseph's/Candler Savannah, GA	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
	Cancer Institute, Maine Medical Center Portland, ME	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
	Northside Cancer Institute, Atlanta, GA	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**
Interim Analysis after 10th Patient is accrued and has finished 3 months post radiotherapy visit	All study sites				**x**								
Final Assessments Complete (3 months post radiotherapy visit)	All study sites									**x**			

Inflammatory Markers	Andrew Miller Laboratory										**x**	**x**	
Gene Expression	Emory Integrated Genomics Core, Office of Jennifer Felger										**x**	**x**	
ctDNA Assay and Analysis	Circulating Tumor Cell Center Massachusetts General Hospital Harvard University Office of Aditya Bardia										**x**	**x**	**x**
Final Data Analysis, reporting, and manuscript submission	Offices of Jeff Switchenko and Mylin Torres											**x**	**x**

*****Numbers reflect estimated total number of patients accrued to the protocol at each site by the end of the indicated quarter but could exceed these numbers for any individual site as long as 42 total subjects are enrolled on the study from all sites. Therefore, numbers of patients enrolled at each specific location could vary accordingly. Peripheral blood draws, Behavioral assessments, clinical and demographic information will be collected at the timepoints indicated in the Schema. IRB approval for all sites will occur during the fourth quarter of 2018 and first and second quarter of 2019. Georgia Cancer Center in Augusta, GA is still working on local IRB approval.

During the second year of this study, abstracts of our findings will be submitted to the annual ASTRO and ASCO conference for presentation. The publication plan is to submit manuscripts of our finding to the *Journal of Clinical Oncology* and International *Journal of Radiation Oncology, Biology, and Physics* at the end of year 3.

Enrollment period: 24 months starting third quarter of 2019. IRB approval for all sites will occur during the fourth quarter of 2018 and first and second quarter of 2019. See above study timelines.

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