ALLIANCE FOUNDATION TRIALS (AFT)

PROTOCOL NUMBER

AFT –38

A Randomized, Open Label, Phase III Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy vs. Anti-HER2 Therapy + Endocrine Therapy after Induction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Breast Cancer

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Investigational Product: Palbociclib
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IND#: 132050
Non-US Sponsor:
EudraCT#: 2017-000419-17
Investigational Product Supplier: Pfizer Inc.

ClinicalTrials.gov Identifier: NCT02947685

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PROTOCOL SIGNATURE PAGE

Protocol Title: PATINA: A Randomized, Open Label, Phase III Trial to Evaluate the Efficacy and Safety of **PA**lbociclib + Anti-HER2 **T**herapy + Endocrine Therapy vs. Anti-HER2 Therapy + Endocrine Therapy after **IN**duction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Bre**A**st Cancer

Protocol Number: AFT-38

FDA IND Number: 132050

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Signatures:

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2/13/2024

Date

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2/13/2024

Date

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Randomized, Open Label, Phase III Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy vs. Anti-HER2 Therapy + Endocrine Therapy after Induction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Breast Cancer

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EudraCT Number: 2017-000419-17

US Sponsor Name: Alliance Foundation Trials (AFT), LLC

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, all applicable regulations, ICH Good Clinical Practice (GCP) and Declaration of Helsinki.

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First Name, Last Name Date, Signature

Study Resources

IRT Randomization System - Oracle accessible via the AFT website, https://alliancefoundationtrials.org
Clinical Database – Mayo Clinic Statistical and Data Center **Medidata Rave® iMedidata** accessible via the AFT portal: [redacted] or [redacted]
AFT Biorepository (AFB) – Washington University **BioMS** accessible via the AFT portal: (https://alliancefoundationtrials.org)
Central Imaging Core Lab – Wright Center of Innovation in Biomedical Imaging **University of Cincinnati** [redacted]

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Synopsis

Study Title	A Randomized, Open Label, Phase III Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy vs. Anti-HER2 Therapy + Endocrine Therapy after Induction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Breast Cancer
Study Number	AFT-38
Study Type/Phase	International, multicenter, open-label, pivotal Phase III study
Clinical Indication	HER2+, HR+ Metastatic Breast Cancer
ClinicalTrials.gov Identifier	NCT02947685
IND Number	132050
Number of Trial Patients	496
Estimated Duration of Trial	9 Years
End of Study	The study will end approximately 5 years after the last patient is randomized.
Rationale	The current study is built on strong pre-clinical and clinical rationale demonstrating the benefits of palbociclib when given in combination with endocrine therapies and anti-HER2 therapies. We expect that the addition of palbociclib to the first-line treatment of HER2 disease will delay the onset of therapeutic resistance and ultimately prolong patient's survival. The study is designed to treat the subset of HER2+ disease classified as hormone receptor positive. We expect that palbociclib will modulate the endocrine resistance in HER2+HR+ disease and also potentiate the benefits of anti-HER2 therapy. Lastly, the current study includes a comprehensive molecular characterization of the disease at the study entrance which will allow us to investigate the benefits of palbociclib in subsets of HER2+ disease such (e.g. PIK3CA mutant).
Primary Objective	The primary objective of this study is to demonstrate that the combination of palbociclib with anti-HER2 therapy plus endocrine therapy is superior to anti-HER2-based therapy plus endocrine therapy in prolonging PFS in participants with hormone receptor-positive, HER2+ metastatic breast cancer who have not received any prior treatment beyond induction treatment in this setting.
Secondary Objectives	1. To compare measures of tumor control (including OR, CBR, DOR) between the treatment arms 2. To compare median overall survival and overall survival probabilities at 3-years and 5-years between the treatment groups

	3. To compare safety and tolerability between the treatment arms 4. To compare the incidence of CNS metastasis between the treatment arms 5. To compare patient reported time to symptom progression as assessed by the FACT-B TOI-PFB 6. To compare patient reported breast cancer specific health related quality of life (HRQOL) and general health status.
Translational Science Objectives	Principal: To compare progression-free survival based upon investigator assessment of progression between patients in the two treatment arms in the subset of patients with tumors bearing a *PIK3CA* mutation. *PIK3CA* genotype will be assessed in circulating tumor DNA (ctDNA) Exploratory: 1. To evaluate PFS and OS in genomically-defined breast cancer subgroups based on pre-specified genomic assays 2. To evaluate baseline tumor- and blood-based markers as predictors of benefit from the addition of palbociclib to anti-HER2 therapy plus endocrine therapy 3. To evaluate tumor- and blood-based markers at time of disease recurrence for mechanisms of resistance to therapy 4. To compare serial levels of circulating tumor DNA (ctDNA) in patients receiving anti-HER2 therapy plus endocrine therapy versus anti-HER2 therapy plus endocrine therapy plus palbociclib 5. To compare mutational profile/copy number variants obtained from tumor tissue to those measured in circulating tumor DNA (ctDNA) 6. To use ctDNA sequencing to compare the inferred tumor transcriptome before and during treatment with anti-HER2 therapy and endocrine therapy with or without palbociclib 7. To determine the trough concentrations of palbociclib when given in combination with trastuzumab plus endocrine therapy or trastuzumab plus pertuzumab plus endocrine therapy 8. To determine trastuzumab and pertuzumab trough concentrations when given in combination with palbociclib plus endocrine therapy 9. To explore correlations between palbociclib exposure and efficacy/safety findings in this patient population 10. To compare the progression-free survival (PFS) outcomes assessed through either local and/or central imaging review with those evaluated using artificial intelligence-based imaging analysis
Primary Endpoint	Progression-free survival (PFS) as assessed by the Investigator
Secondary Endpoints	1. Overall Survival (OS) 2. 3-year and 5-year survival probabilities 3. Objective response (OR: CR or PR) 4. Duration of response (DOR) 5. Clinical Benefit Rate (CBR: CR or PR or SD ≥ 24 weeks) 6. Incidence of CNS metastasis

	7. Safety: Type, incidence, severity (as graded by the NCI CTCAE v. 4.0), seriousness and attribution to the study medications of AEs and any laboratory abnormalities 8. Patient Reported Outcomes: Time to symptom progression (FACT-B PFB-TOI), breast cancer specific health treatment related quality of life and general health status
Correlative Endpoints	1. Trough plasma concentration of palbociclib, trastuzumab and pertuzumab in the subgroup of patients enrolled in the US 2. *PIK3CA* genotype assessed in circulating tumor DNA (ctDNA) 3. Tumor tissue biomarkers including genes, proteins, and RNA expression
Inclusion Criteria	Inclusion Criteria (Preliminary Screening) 1. Signed Preliminary Screening Informed Consent Form obtained prior to any study specific assessments and procedures 2. Age ≥18 years (or per national guidelines) 3. Participants must have histologically confirmed invasive breast cancer that is metastatic or not amenable for resection or radiation therapy with curative intent. Histological documentation of metastatic/recurrent breast cancer is not required if there is unequivocal evidence for recurrence of the breast cancer. 4. Patients must have histologically confirmed HER2+ and hormone receptor positive (ER+ and/or PR+), metastatic breast cancer. ER, PR and HER2 measurements should be performed according to institutional guidelines, in a CLIA-approved setting in the US or certified laboratories for Non-US regions. Cut-off values for positive/negative staining should be in accordance with current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines. 5. Patients must agree to provide a representative formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) from primary breast or metastatic site (archival) *OR* at least 15 freshly cut unstained slides from such a block, along with a pathology report documenting HER2 positivity and hormone receptor positivity. 6. Patients should be willing to provide a representative tumor specimen obtained from recently biopsied metastatic disease if clinically feasible. This is recommended but optional tissue. Inclusion Criteria (Randomization Screening) 7. Signed Main Informed Consent Form obtained prior to any study specific assessments and procedures 8. Age ≥ 18 years (or per national guidelines) 9. ECOG performance status 0-1 10. Patients must be able and willing to swallow and retain oral medication without a condition that would interfere with enteric absorption. 11. Serum or urine pregnancy test must be negative within 7 days of randomization in women of childbearing potential. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation. Women of childbearing potential and male

patients randomized into the study must use adequate contraception for the duration of protocol treatment which is for 6 months after the last treatment with palbociclib if they are in Arm A and for 7 months after last treatment with trastuzumab if in either Arm A or Arm B. Adequate contraception is defined as one highly effective form (i.e. abstinence, (fe)male sterilization OR two effective forms (e.g. non-hormonal IUD and condom / occlusive cap with spermicidal foam / gel / film / cream / suppository).

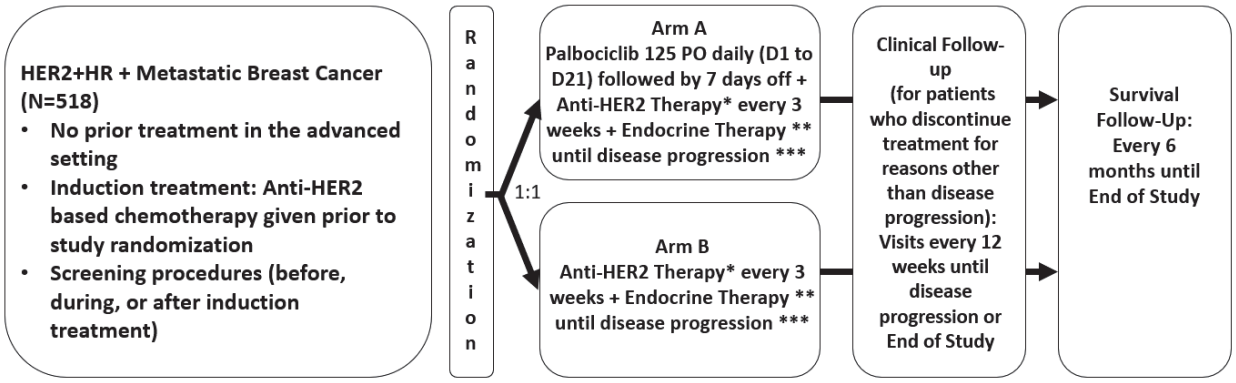
12. Resolution of all acute toxic effects of prior induction anti-HER2-based chemotherapy regimen to NCI CTCAE version 4.0 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion) 12 weeks between last dose of chemotherapy–anti-HER2therapy and randomization are allowed. Endocrine therapy could start before study randomization.
13. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

Prior Treatment Specifics

14. Patients may or may not have received neo/adjuvant therapy, but must have a disease-free interval from completion of anti-HER2 therapy to metastatic diagnosis ≥6 months.
15. Patients must have received an acceptable, standard, chemotherapy containing anti-HER2 based induction therapy for the treatment of metastatic breast cancer prior to study enrollment. For this study, chemotherapy is limited to a taxane or vinorelbine (only for trastuzumab-based regimen). Eligible patients are expected to have completed 6 cycles of chemotherapy containing anti-HER2-therapy treatment. A minimum of 4 cycles of treatment is acceptable for patients experiencing significant toxicity associated with treatment as long as they are without evidence of disease progression (i.e. CR, PR or SD). The maximum number of cycles is 8. Patients can randomize immediately following completion of their induction therapy, or for those who have already completed induction, a gap of 12 weeks between their last infusion/dose of induction therapy and the C1D1 visit is permitted. Patients are eligible provided they are without evidence of disease progression by local assessment (i.e. CR, PR or SD).
16. Patients with a history or presence of asymptomatic CNS metastases are eligible provided they meet all of the following criteria:
    - Disease outside the CNS is present.
    - No evidence of interim progression between the completion of induction therapy and the screening radiographic study
    - No history of intracranial hemorrhage or spinal cord hemorrhage
    - Not requiring anti-convulsants for symptomatic control
    - Minimum of 3 weeks between completion of CNS radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade ≥ 3) acute toxicity with no ongoing requirement for corticosteroid

	Baseline Body Function Specifics 17. Absolute neutrophil count ≥ 1,000/mm3 18. Platelets ≥ 100,000/mm3 19. Hemoglobin ≥ 10g/dL 20. Total serum bilirubin ≤ ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert's Syndrome. 21. Aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) ≤ 3 × institutional ULN (≤5 x ULN if liver metastases are present). 22. Serum creatinine below the upper limit of normal (ULN) of the institutional normal range or creatinine clearance ≥ 60 mL/min/1.73 m2 for patients with serum creatinine levels above institutional ULN. 23. Left ventricular ejection fraction (LVEF) ≥ 50% at baseline as determined by either ECHO or MUGA
Exclusion Criteria	Exclusion Criteria (Randomization) 1. Concurrent therapy with other Investigational Products. 2. Prior therapy with any CDK 4/6 inhibitor. 3. History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib. 4. Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A isoenzymes within 7 days of randomization (see Section 8.6.3 for list of strong inhibitors or inducers of CYP3A isoenzymes). 5. Uncontrolled current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, or psychiatric illness/social situations that would limit compliance with study requirements. Ability to comply with study requirements is to be assessed by each investigator at the time of screening for study participation. 6. Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to randomization, irrespective of the method of contraception used, are excluded from this study because the effect of palbociclib on a developing fetus is unknown. Breastfeeding must be discontinued prior to study entry. 7. Patients on combination antiretroviral therapy, i.e. those who are HIV-positive, are ineligible because of the potential for pharmacokinetic interactions or increased immunosuppression with palbociclib. 8. QTc interval >480 msec, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes. 9. Patients with clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis

Study Schema



* Anti-HER2 treatment options are Trastuzumab plus Pertuzumab or Trastuzumab only (limited to 20% of the study population). The same anti-HER2-regimen should be used before and post randomization.

** Endocrine therapy options are either an Aromatase Inhibitor or Fulvestrant. Premenopausal women must receive ovarian suppression with a LHRH agonist if the patients have not documented ovarian ablation or bilateral oophorectomy before randomization or during the conduct of the study.

1. Introduction

This is a randomized, open-label, multicenter, Phase III trial to assess the safety and efficacy of palbociclib plus anti-HER2 therapy and endocrine therapy vs. anti-HER2 therapy plus endocrine therapy for hormone receptor positive / HER2+ metastatic breast cancer.

1.1 Background and Rationale

Breast cancer remains the most frequently diagnosed cancer in women and is the leading cause of cancer-related death worldwide. Despite significant improvements in the treatment of early-stage breast cancer, approximately 30 percent of women experience metastatic disease relapse [1]. Surprisingly, data from the Surveillance, Epidemiology, and End Results (SEER) program show that the incidence of metastatic breast cancer has been stable since 1975. The lack of change in the incidence of metastatic disease supports the notion that breast cancer is a systemic disease [2]. This concept is supported by the fact that approximately 5% of women diagnosed with breast cancer have evidence of metastatic disease at the time of diagnosis (de novo presentation) despite the advances in screening techniques. In consonance with previous findings, data from SEER show no signs of decline in the incidence of de novo metastatic breast cancer over the past three decades. While metastatic breast cancer remains an incurable disease, it is important to stress that the development of novel therapies for the treatment of metastatic breast cancer should be considered a high priority.

In light of the evolving breast cancer classification, HER2+ breast cancer has emerged as a separate disease entity and the development of therapies targeting the HER2 receptor has dramatically improved patient outcomes. During the first decade of trastuzumab use for advanced HER2+ breast cancer, a significant improvement in the understanding of the biology of HER2+ disease led to the development and approval of novel anti-HER2 agents. Pertuzumab is a monoclonal antibody similar to trastuzumab with the ability to block HER2 function as a co-receptor, thus inhibiting HER2 heterodimerization with other members of HER family (e.g., HER1, HER3). The efficacy of pertuzumab was evaluated in a Phase 3 study called CLEOPATRA (Clinical Evaluation Of Pertuzumab And Trastuzumab) [3, 4].

Despite significant improvements, HER2+ breast cancer is still a serious and life-threatening disease. Patients with distant disease recurrence after treatment of HER2+ disease, along with patients with metastasis at diagnosis, eventually progress and die of breast cancer despite the availability of chemotherapy, endocrine therapy and anti-HER2 therapy. Of the 450,000 global deaths from breast cancer each year [5] around 15% to 20% (60,000~90,000) are likely to be due to HER2+ disease. This translates to around 12,000 to 15,000 deaths per annum in Europe and 6,000 to 8,000 deaths per annum in the US.

In order to improve beyond the current standards, it is important to highlight the major limitations of available therapies: 1) Patients with advanced disease inevitably develop resistance to anti-HER2 therapies; 2) Tumor heterogeneity within HER2+ disease is now evident and can be divided into two major subtypes according to the expression of hormone receptor status; 3) Specific subsets of HER2+ disease (e.g. somatic PIK3CA mutation) have a particularly unfavorable outcome when treated with conventional chemotherapy. Taking together these factors point to the need for clinical studies dedicated to specific subsets of HER2+ disease.

The current study is built on strong pre-clinical and clinical rationale demonstrating the benefits of palbociclib when given in combination with endocrine therapies and anti-HER2 therapies. We expect that the addition of palbociclib to the first-line treatment of HER2 disease will delay the onset of therapeutic resistance and ultimately prolong patient's survival. The study is designed to treat the subset of HER2+ disease that also expresses hormone receptor status. We expect that palbociclib will modulate the endocrine resistance in HER2+ER+ disease and also potentiate the benefits of anti-HER2 therapy. Lastly, the current study includes a comprehensive molecular characterization of the disease at the study entrance which will allow us to investigate the benefits of palbociclib in subsets of HER2+ disease such (e.g. *PIK3CA* mutant).

1.2 Overview of Palbociclib

1.2.1 Palbociclib Mechanism of Action

Cell cycle inhibition is a target of choice for novel cancer therapeutics. Palbociclib (PD-0332991, Ibrance®), an orally active pyridopyrimidine, is a potent first-in-class, highly selective reversible inhibitor of CDK 4 and CDK6 (IC50 = 11 nM; Ki = 2 nM) with a molecular weight of 447.53. Data from nonclinical studies indicate that palbociclib may have cytoreductive as well as cytostatic effects on tumor cells. A complete description of the activity and safety of palbociclib can be found in the investigators brochure [6].

The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials. CDK4 and CDK6 control G1 to S phase transit by binding to D-type cyclins [7-9]. The CDK4/6/Cyclin

D1(CCND1)complex phosphorylates the retinoblastoma susceptibility (RB1) gene product (Rb), releasing the E2F and DP transcription factors that drive expression of genes required for S-phase entry[9]. CDK activity and G1 progression is negatively regulated by Cip-Kip and INK4 family, typified by p16[10-14]. Overexpression of p16 in cells with normal Rb inhibits both CDK4-and CDK6-associated kinase activity and Rb phosphorylation, with subsequent cell cycle arrest [15, 16].

1.2.2 Preclinical Rational for Use of Palbociclib in HER2+ER+Positive Breast Cancer

It is known that CCND1 is downstream of HER2 and plays a critical role in HER2 transformation [17-19]. In preclinical studies, the association between HER2 signaling and regulation of CCND1-CDK complexes has been established [17-19]. Relatively simple cellular models of HER2-mediated transformation showed that CCND1/CDK4-6 activity was essential for this process [20]. These findings were further expanded on with a transgenic mice model overexpressing HER2 in the mammary gland that develops HER2 driven breast cancer on a predictable schedule. Reducing retinoblastoma protein (Rb) phosphorylation through CDK4 knock-out or p16 overexpression is sufficient to block development of tumorigenesis in this model [21, 22]. Studies conducted at Sicinski and Hinds laboratories further illustrated the relationship between elevation of CCND1 and HER2 amplification/overexpression in clinical specimens and refined the requirement of CCND1/CDK4 activity in HER2 driven breast cancer models [19, 23].

In preclinical studies, HER2+ cell lines, such as MDA-MB-361 and BT474 were sensitive to palbociclib. In addition, palbociclib has been shown to have synergistic antitumor activity when combined with trastuzumab [24]. Witkiewicz et al have demonstrated in preclinical HER2+ models that palbociclib had potent cell cycle inhibitory activity and specifically suppressed long-term proliferation in cells resistant to anti-HER2 treatment [25]. The interaction between CDK4/6 inhibition and established HER2 inhibitors has been evaluated in this study, and the data indicated that CDK4/6 inhibition has a complementary effect to anti-HER2 targeted agents. In particular, the potent cytostatic activity and induction of senescence properties of palbociclib reduced the number of vital cells at limiting dose of anti-HER2 therapy. More recent work with a transgenic HER2 mouse model has described significant tumor growth inhibition when treated with palbociclib [26]. Finally, recently published work in Cancer Cell describes the role of CDK4/6 activity in driving resistance to HER2 targeted therapy [27]. In this context CDK4/6 signaling relieves feedback inhibition on the mTOR pathway and progression through the cell cycle. Inhibition of CDK4/6 with abemaciclib suppresses phosphorylation of Rb and mTOR substrates when combined with HER2 inhibitors and sensitizes patient derived xenografts to this therapy while delaying tumor recurrence.

Data from extensive preclinical work demonstrates that the CCND1/CDK4 complex mediates resistance to HER2-targeted therapies [27]. Using novel transgenic mouse models, cell-line based functional assays, and patient-derived xenografts (PDX), the authors demonstrated that CDK4/6 inhibition re-sensitizes resistant HER2+ breast cancers to anti-HER2 therapies. Indeed, PDX tumors derived from anti-HER2 refractory tumors show tumor regression when treated with CDK4/6 inhibition plus anti-HER2 therapy. This occurs because CDK4/6 inhibitors not only suppress Rb phosphorylation, but also relieve feedback inhibition of upstream receptor tyrosine kinases (including HER2 and HER3). This leads to a re-sensitization of tumor cells to

HER2-targeting such that combined treatment induces a maximal suppression of P70S6-kinase activity. Collectively, the suppression of both Rb and S6RP phosphorylation induces a pronounced G1 arrest in tumor cells.

1.2.3 Palbociclib Pharmacokinetic (PK) Data in Humans

Pharmacokinetic (PK) data from patients with advanced cancer from Study A5481001 indicate that the plasma pharmacokinetics of palbociclib are low to moderately variable with generally dose proportional exposures over the dose range evaluated (25 mg to 225 mg). PK data from Studies A5481001, A5481003, and A5481010 indicate that palbociclib is slowly absorbed with a median time of maximum concentration (Tmax) between 4 and 8 hours post-dose, and is slowly eliminated with an elimination half-life (t1/2) ranging from 23.2 hours to 28.8 hours. Palbociclib accumulates after repeated daily dosing (median Rac ranged from 1.9 to 2.4), which was consistent with its terminal t1/2. In Study A5481010, the median Rss (the predicted accumulation to estimate linearity) was 1.1, indicating that palbociclib clearance does not change over time. In Study A5481003, palbociclib was shown to achieve steady-state concentrations following 8 days of QD dosing. The palbociclib geometric mean volume of distribution (Vz/F) was 2583 L in women with advanced breast cancer (Study A5481003), which is significantly greater than total body water (42 L), indicating that palbociclib extensively distributes to peripheral tissues.

In humans, metabolism is the major route of elimination of palbociclib. Following a single oral administration of [14C] palbociclib to healthy subjects (Study A5481011), the overall median recovery of the administered radioactivity in the excreta was 91.6% with a median of 17.5% recovered in urine and a median of 74.1% recovered in feces. Excretion of unchanged palbociclib in the feces and urine was 2.3% and 6.9% of dose, respectively, indicating that excretion plays a minor role in elimination of palbociclib. A study in healthy volunteers (A5481015) indicated that the absolute oral bioavailability of palbociclib was approximately 46%.

In vitro data indicate that CYP3A and SULT enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

In vitro data indicate that palbociclib has a low potential for inhibiting the activities of selected uridine diphosphate glucuronosyltransferase (UGT) enzymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) and transporters (P-gp [systemically], BCRP [systemically], OATP1B1, OATP1B3, BSEP, OAT1, OAT3, and OCT2) at clinically relevant concentrations. However, palbociclib has the potential to inhibit the intestinal efflux transporters P-gp and BCRP, and the hepatic uptake transporter OCT1.

An itraconazole Drug-Drug Interaction (DDI) study in healthy volunteers (Study A5481016) and a rifampin DDI study in healthy volunteers (Study A5481017) were conducted to evaluate the potential for strong CYP3A inhibitors and inducers, respectively, to alter the PK of palbociclib. Co-administration of itraconazole and palbociclib increased palbociclib Area Under the Curve (AUC)inf and Cmax by approximately 87% and 34%, respectively, relative to those when palbociclib dose was given alone. Co-administration of rifampin and palbociclib decreased palbociclib AUCinf and Cmax by approximately 85% and 70%, respectively, relative to

palbociclib given alone. Based on this data, the concurrent administration of strong CYP3A inhibitors and inducers with palbociclib should be avoided.

A midazolam DDI study in healthy volunteers (Study A5481012) was conducted to evaluate the potential for palbociclib to act as a time-dependent inhibitor of CYP3A4/5 at steady-state. Plasma midazolam Cmax and AUCinf values increased 37% and 61%, respectively, when single oral doses of midazolam were co-administered with multiple doses of palbociclib as compared to its administration alone. This is consistent with weak time-dependent CYP3A4/5 inhibition mediated by palbociclib at steady-state following daily 125 mg dosing.

PK data from the Phase 1 portion of Study A5481003 was analyzed to evaluate the potential for a DDI between palbociclib and letrozole at steady-state. These data indicate a lack of a potential for DDIs between palbociclib and letrozole when administered in combination.

Data from a DDI study in healthy male subjects indicated that palbociclib exposures were comparable when a single dose of palbociclib was co-administered with multiple doses of tamoxifen and when palbociclib was given alone.

The effect of food on the exposure of palbociclib, when administered as the commercial free base capsule, was evaluated in healthy subjects (A5481021). Compared to palbociclib given under overnight fasted conditions, the AUCinf and Cmax of palbociclib increased by 21% and 38% when given with high-fat food, by 12% and 27% when given with low-fat food, and by 13% and 24% when moderate-fat food was given 1 hour before and 2 hours after palbociclib dosing. In addition, food intake significantly reduced the intersubject and intrasubject variability of palbociclib exposure. Based on these results, palbociclib commercial free base capsules should be taken with food.

The solubility of the palbociclib free base is pH dependent—palbociclib is water soluble at low pH (2.1-4.5), while the solubility dramatically decreases as pH rises above 4.5. Concomitant administration of agents which increase gastric pH can alter the solubility and absorption of palbociclib free base formulations.

In a drug interaction trial in healthy subjects (A5481038), co-administration of a single 125 mg dose of commercial free base capsule with multiple doses of the proton pump inhibitors (PPI) rabeprazole under fed conditions decreased palbociclib Cmax by 41%, but had limited impact on AUCinf (13% decrease), when compared to a single dose of palbociclib administered alone. Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid-reducing agents on palbociclib exposure under fed conditions is expected to be minimal. Under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists, or local antacids on palbociclib exposure. In another healthy subject study, co-administration of a single dose of commercial free base capsule with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUCinf and Cmax by 62% and 80%, respectively, when compared to a single dose of palbociclib administered alone. Collectively, these antacid DDI data further support the requirement that the free base capsule of palbociclib should be taken with food.

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age range from 22 to 89 years, and body weight range from 37.9 to 123 kg), gender had no effect on the exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

Based on a population pharmacokinetic analysis that included 183 patients, where 40 patients had mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST), but are currently being investigated in Study A5481013 (ongoing).

Based on a population pharmacokinetic analysis that included 183 patients, where 73 patients had mild renal impairment (60 mL/min ≤ CrCl <90 mL/min) and 29 patients had moderate renal impairment (30 mL/min ≤ CrCl <60 mL/min), mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with severe renal impairment but are currently being investigated in Study A5481013 (ongoing).

In a substudy from Study A5481008 that was conducted as the definitive QT interval prolongation evaluation for the palbociclib program, triplicate ECGs were collected at clock time-matched baselines and at 5 time points (pre-dose and at 2, 4, 6, and 8 hours postdose) after palbociclib had reached steady-state concentrations following a therapeutic dosing schedule (125 mg QD on Schedule 3/1 in combination with letrozole). A total of 77 patients were enrolled for intensive QTc assessment in the palbociclib plus letrozole arm within the QT interval prolongation substudy, and 76 patients provided post-dose ECG data. A random-effect analysis of the ECG data from this substudy demonstrated that the upper bounds of the 1-sided 95% CIs for the mean changes from clock time-matched baseline for QTcF, QTcS, and QTcB were <8 msec at all 5 time points in the QTc assessment period. In addition, pharmacokinetic/pharmacodynamic analyses to evaluate the relationship between palbociclib exposure and ECG endpoints (RR and QTc intervals) were developed using the same ECG data along with the time-matched PK data. There was no significant relationship between palbociclib concentrations and RR interval, suggesting that palbociclib does not appear to have a concentration dependent effect on the heart rate. There was a slight positive linear relationship was observed between palbociclib concentration and QTcS. At the mean steady-state palbociclib C_{max}, the mean QTcS increase was 4.04 msec, with the upper bound of the 1-sided 95% CIs falling below 10 msec. Similar results were obtained when QTcF and QTcB were used. Both of these analyses indicate that palbociclib, when added to letrozole, did not prolong QT interval to a clinically meaningful extent.

The proposed study will evaluate treatment with palbociclib plus anti-HER2 therapy plus endocrine therapy compared with anti-HER2 therapy plus endocrine therapy. The anti-HER2 therapies include 1) trastuzumab, and/or 2) pertuzumab. In the current study, the choices of endocrine therapy are either an aromatase inhibitor (AI), (i.e. anastrozole, letrozole or exemestane) or Fulvestrant.

The potential for a clinically significant DDI between palbociclib and trastuzumab is considered to be low. In general, therapeutic proteins (including trastuzumab) are not expected to have a direct effect on the metabolic pathway or pharmacodynamics of concomitantly administered medications (and vice versa). The most well documented therapeutic protein-caused DDI is via indirect mechanism, involving cytokine-mediated changes in drug-metabolizing enzymes. This is due to suppression of cytochrome P450 enzyme levels by inflammatory cytokines; whereas, the anti-cytokine therapies can “normalize” P450 level and as a result, alter clearance of drugs which are metabolized by P450 enzymes. For example, cytokines such as IL-6 can produce

concentration-dependent inhibition on various CYP isoforms at the transcription level or by alteration of CYP enzyme stability in patients with infection or inflammation, and increase the plasma concentrations of specific CYP substrate drugs. In contrast, cytokine modulators such as tocilizumab (anti-IL-6 receptor antibody) may reverse the apparent "inhibition" effect of the cytokines on CYP substrates, resulting in a "normalization" of CYP activities. Trastuzumab was not known to be a cytokine modulator, thus the probability of trastuzumab to affect the clearance of palbociclib is low.

For therapeutic proteins (TPs), clearance often undergoes an array of specific target-mediated, immunogenicity-mediated, and/or non-specific receptor-mediated endocytosis mechanisms. TPs typically do not undergo metabolism or transport as their clearance pathway, therefore the potential is limited for small molecule drugs to affect TPs through metabolism or transport pathways. However, a drug may affect the clearance of TPs through the drug's effect on immunogenicity (e.g., methotrexate reduces the clearance of infliximab, possibly due to methotrexate's effect on the antibodies formed against infliximab). Palbociclib has not shown to affect the host immune system, thus the probability of palbociclib to affect the PK of trastuzumab is low.

1.2.4 Palbociclib and Endocrine Therapy Pharmacokinetics

Results from the Phase I portion of PALOMA-1 indicated no PK interaction between palbociclib and letrozole with mean AUC (0-24) of 2002 and 2043 ng•hr/mL (n=11) for palbociclib in the absence and presence of letrozole.

The potential for a DDI between palbociclib and tamoxifen is considered to be probable based on in vitro data. Multiple enzymes are responsible for the metabolism of tamoxifen and its active metabolites including CYP3A4, CYP2C9, and CYP2D6. In vitro evidence suggest that tamoxifen and one of its primary active metabolites, 4-hydroxy-tamoxifen, are inducers of CYP3A4 enzymes. In clinical trials, co-administration of tamoxifen with letrozole and anastrozole (both CYP3A4 substrates) has resulted in decreased exposures (AUC) of each by 37% and 27%, respectively. Palbociclib is a CYP3A4 substrate and CYP3A4 is thought to be the primary route of the oxidative metabolism of palbociclib. Thus, the co-administration of tamoxifen and palbociclib may lead to lower circulating levels of palbociclib and require an upward dose adjustment in palbociclib if these two compounds are used in conjunction. Additionally, time-dependent inhibition of CYP3A4 has been observed in preclinical studies of palbociclib.

The effect of multiple dosing of tamoxifen (60 mg QD for 4 days followed by 20 mg QD for 23 days), on the single-dose PK of palbociclib (125 mg), was evaluated in 25 healthy fasted subjects in Study A5481026. Administration of palbociclib in the presence of tamoxifen and its metabolites (4-hydroxy-tamoxifen, N-desmethyl-tamoxifen, and 4-hydroxy-N-desmethyl-tamoxifen) at steady state showed that palbociclib exposure was comparable with that when palbociclib was given alone. The ratios (90% CIs) of the adjusted geometric means of palbociclib AUCinf and Cmax were 108% (104%-111%) and 116% (105%-129%), respectively, following administration of palbociclib with multiple doses of tamoxifen (Test) relative to palbociclib administered alone. These results indicate that it is not necessary to adjust palbociclib starting dose when co-administering with tamoxifen[6]. A two-way DDI assessment between palbociclib and tamoxifen in cancer patients has been incorporated into the ongoing PENELOPE-B Study (ClinicalTrials.gov NCT01864746).

The potential for a clinically significant DDI between palbociclib and anastrozole is considered to be low. Anastrozole inhibited CYP1A2, 2C8, 2C9, and 3A4 in vitro with Ki values ~30-fold higher than the steady-state Cmax values observed following a 1mg daily dose. In vitro and in vivo assessments of oxidative metabolism have indicated the route of formation of the primary metabolite hydroxyanastrozole is predominantly through CYP3A4. Time dependent inhibition of CYP3A4 has been observed in in vitro studies of palbociclib, thus palbociclib has the potential to inhibit the primary clearance pathway of anastrozole. A two-way DDI assessment between palbociclib and anastrozole has been incorporated into the ongoing PENELOPE-B Study (ClinicalTrials.gov NCT01864746).

The potential for a clinically significant DDI between palbociclib and exemestane is considered to be very low. Exemestane is metabolized by cytochrome P 450 3A4 (CYP 3A4) and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1, and 3A4. Therefore, exemestane is unlikely to affect palbociclib PK. Rifampin reduced exemestane exposure by ~50%. However, in a clinical pharmacokinetic study, co-administration of ketoconazole, a potent inhibitor of CYP 3A4, had no significant effect on exemestane pharmacokinetics. Therefore, it is unlikely that palbociclib, which is a weak time-dependent inhibitor of CYP34, will have an effect on exemestane PK. A two-way DDI assessment between palbociclib and exemestane has been incorporated into the ongoing PEARL Study (ClinicalTrials.gov NCT02028507).

The potential for a clinically significant DDI between palbociclib and goserelin is considered to be very low. Goserelin is a synthetic decapeptide analogue of gonadotropin releasing hormone (GnRH) whose primary route of elimination is the cleavage of C-terminal amino acids followed by renal excretion. No formal DDI studies have been performed and no confirmed interactions have been reported between goserelin and other drugs. A DDI assessment between palbociclib and goserelin has been included into two ongoing studies; A5481023 and the PENELOPE-B Study.

1.2.5 Preclinical Data – Palbociclib

1.2.5.1 Overview of Nonclinical Efficacy Data

Palbociclib preclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytoreductive activity. Single agent palbociclib has showed antiproliferative effects (selective G1 arrest) on Rb-positive cancer cells *in vitro* and *in vivo* where palbociclib activity was associated with reduced Rb-phosphorylation and decreased expression of the cell proliferation marker Ki67.

Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific pRb phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of pRb. The IC_{50} values for reduction of pRb phosphorylation at serine -780 and -795 in MDA-MB-435 breast carcinoma cells were 0.066 and 0.063 μM, respectively. The IC_{50} values for reduction of pRb phosphorylation are similar to the IC_{50} values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

Palbociclib was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to palbociclib (IC_{50} <150 nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell

lines show the opposite characteristics. Sensitive cell lines in this panel represent mostly the luminal ER-positive subtype.

The combination of palbociclib with tamoxifen has been tested in vitro in ER-positive human breast cancer cell lines indicating a synergistic interaction and provided a biologic rationale for evaluating the combination of palbociclib with anti-hormonal therapy in the clinic.

1.2.5.2 Overview of Nonclinical Safety Data

The nonclinical safety profile of palbociclib has been well characterized through the conduct of single- and repeat-dose toxicity studies up to 39 weeks in duration, and safety pharmacology, genetic toxicity, reproductive and developmental toxicity, and phototoxicity studies.

Consistent with the pharmacologic activity of palbociclib (cell cycle inhibition, CDK4/6 inhibition), the primary target organ findings included hematolymphopoietic (decreased cellularity of bone marrow and lymphoid organs) and male reproductive organ (seminiferous tubule degeneration, and secondary effects on the epididymis, prostate, and seminal vesicle) effects in rats and dogs, and altered glucose metabolism that was accompanied by effects on the pancreas and secondary changes in the eye, kidney, and adipose tissue in rats only, and effects on bone and growing incisor tooth in rats only that were observed following single and/or repeat dosing at clinically relevant exposures. Altered glucose metabolism (hyperglycemia/glucosuria) correlated with pancreatic islet cell vacuolation that was determined to reflect a loss of beta cells with corresponding decreases in insulin and C-peptide. The reversibility of the effects on glucose homeostasis, pancreas, eye, kidney, and bone was not established following a 12-week non-dosing period; whereas partial to full reversal of effects on the hemato-lymphopoietic and male reproductive systems, teeth, and adipose tissue were observed.

Additionally, a potential for QTc prolongation and hemodynamic effects were identified from safety pharmacology studies, and developmental toxicity was identified from embryo-fetal development studies in the rat and rabbit.

Though gastrointestinal effects would be anticipated from a cell cycle inhibitor and while effects were observed in rats and dogs following single- and repeat-dose studies up to 3 weeks in duration (emesis, fecal changes, and microscopic changes in stomach and intestines), the effects were of limited severity at clinically relevant doses. Gastrointestinal effects were not prominent in longer duration studies, limited to effects on the glandular stomach and rodent-specific effects on the non-glandular stomach in rats following 27 weeks of intermittent dosing that did not reverse during a 12-week non-dosing period. Additional palbociclib-related findings considered non-adverse at tolerated doses based on limited severity and/or absence of degenerative changes included cellular vacuolation in multiple tissues that was morphologically consistent with phospholipidosis; hepatic (increases in liver enzymes, hepatocellular hypertrophy/increased vacuolation), renal (increased chronic progressive neuropathy), adrenal (cortical cell hypertrophy), and respiratory (clinical signs, tracheal epithelial cell atrophy) effects; and prolonged coagulation times. Reversibility (partial or full) was established for these additional toxicities. Finally, palbociclib was determined to be an aneugen, for which a no effect exposure was identified. Additional information may be found in the IB for palbociclib.

1.2.6 Clinical Data – Palbociclib

1.2.6.1 Palbociclib Clinical Data in Breast Cancer

Palbociclib has been tested in a Phase 1 dose escalation trial (Study A5481001) in 74 patients with advanced cancer. Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on treatment followed by 1 week off treatment; n=41) at doses ranging from 25 to 150 mg and Schedule 2/1 (2 weeks on treatment followed by 1 week off treatment; n=33) at doses ranging from 100 to 225 mg. All dose limiting toxicities (DLTs) observed in this study were related to myelosuppression and mainly consisted of Grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, neutropenia was reversible and non-cumulative. The most common non-hematological adverse events (AEs) included fatigue, anemia, diarrhea, constipation, vomiting, and dyspnea, mostly mild to moderate severity. A greater proportion of patients on Schedule 2/1 had treatment-related AEs during and after Cycle 1 than patients on Schedule 3/1 although the proportion of patients with treatment-related neutropenia was similar with respect to the 2 dosing schedules, both during and after Cycle 1. A total of 13/37 patients on Schedule 3/1 evaluable for efficacy experienced stable disease (SD), including 6 patients with SD lasting 40 weeks or longer. Based on the relatively improved safety profile of Schedule 3/1 and the efficacy results, Schedule 3/1 was selected for further clinical development and the Recommended Phase 2 Dose (RP2D) for this schedule was determined to be 125 mg/day.

Palbociclib has been investigated in the following pivotal studies for the treatment of advanced breast cancer: A5481003 (Study 1003), A5481008 (Study 1008), and A5481023 (Study 1023).

Study 1003 was a Phase 1/2, randomized, open-label study designed to assess the efficacy and safety of palbociclib (125 mg QD on Schedule 3/1) in combination with letrozole 2.5 mg QD versus letrozole 2.5 mg QD alone for the first-line treatment of post-menopausal women with ER-positive/HER2-negative advanced breast cancer. The results from the study demonstrated a statistically significant improvement in PFS for the palbociclib plus letrozole arm compared to the letrozole alone arm (20.2 vs. 10.2 months; HR=0.488 [95% CI: 0.319, 0.748]; p <0.001) [28]. The most common AEs reported for the palbociclib plus letrozole arm were hematologic events, mostly neutropenia and leukopenia that were reversible. Based on the results from this study, palbociclib was granted accelerated approval in the US in combination with letrozole for the treatment of post-menopausal women with ER-positive/HER-2 negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

Study 1008 was a Phase 3, randomized, double-blind, placebo-controlled study designed to assess the efficacy and safety of palbociclib (125 mg QD on Schedule 3/1) plus letrozole 2.5 mg QD versus placebo plus letrozole 2.5 mg QD for the first-line treatment of post-menopausal women with ER-positive/HER2-negative advanced breast cancer. The results from the study demonstrated a statistically significant improvement in PFS for the palbociclib plus letrozole arm compared to the placebo plus letrozole arm (24.8 vs. 14.5 months; HR=0.58 [95% CI: 0.46, 0.72]; p <0.000001) [29] confirming the significant clinical benefit and safety of palbociclib plus letrozole in ER-positive/HER2-negative advanced breast cancer who had not received prior systemic therapy for their advanced disease observed in Study 1003 [28].

Study 1023 was a Phase 3, randomized, double-blind, placebo-controlled study designed to assess the efficacy and safety of palbociclib (125 mg QD on Schedule 3/1) plus fulvestrant 500 mg versus placebo plus fulvestrant 500 mg for the treatment of women with HR-positive/HER2-negative advanced breast cancer whose disease had progressed after prior endocrine therapy. The

results from the study indicated that the addition of palbociclib to fulvestrant significantly prolongs PFS with the median PFS of 9.5 months (95% CI: 9.2, 11.0) for the palbociclib plus fulvestrant arm and 4.6 months (95% CI: 3.5, 5.6) for the placebo plus fulvestrant arm (HR=0.461 [95% CI: 0.360, 0.591]; p <0.0001) [30]. The AEs observed in the study were consistent with the known safety profile of palbociclib. Overall, palbociclib was well tolerated with AEs managed by dosing interruptions, dose reductions, and/or standard medical care. Based on the results from this study, palbociclib was approved in the US in combination with fulvestrant for the treatment of women with HR-positive/HER2-negative advanced breast cancer with disease progression following endocrine therapy.

1.2.6.2 Palbociclib Clinical Data in HER2+ Breast Cancer

As mentioned above, in preclinical studies in HER2+ models, palbociclib has been shown to have synergistic antitumor activity when combined with trastuzumab and not only prevented proliferation, but also limited the invasive potential of cells [25]. In addition, a preclinical PDX model demonstrated that CDK4/6 inhibition re-sensitizes resistant HER2+ breast cancers to anti-HER2 therapies [27]. Furthermore, the published data suggest that it is rare for HER2+ tumors to exhibit loss of Rb function [30]. The TCGA data also showed Rb mutation occurs at a much lower rate in ER+/HER2+ (at <5%) as compared to ER-negative/HER2+ (at 25%). These preclinical data provide the impetus to investigate palbociclib in HER2+ breast cancer.

There are 4 ongoing independent Investigator Sponsored Phase Ib and Phase II clinical studies of palbociclib in HER2+ metastatic and early breast cancer (Table). As of the end of February 2016, approximately 70 patients have been treated in 4 clinical trials with palbociclib in combination with various anti HER2 agents in patients with HER2+ early stage and metastatic breast cancer. This includes combination of palbociclib with trastuzumab with or without endocrine therapy (Studies NCT01037790 and NCT02448420), with T-DM1 (Study NCT01976169), and with trastuzumab plus pertuzumab plus endocrine therapy (Study NCT02530424).

Interim information from palbociclib in combination with anti-HER2 therapy indicates encouraging signals of activity. Data to date on these 72 patients show the most commonly reported AEs were hematological toxicities, similar to the known safety profile of single agent palbociclib or palbociclib in combination with endocrine therapy in hormone receptor-positive, HER2-negative disease. No unexpected serious AE reports on anti-HER2- therapy have been received.

Table 1. Ongoing Studies in HER2+ Breast Cancer

Study Title (Tracking No)	Country	Treatment Setting	Regimen	Schedule/ Dosage	Numbers of Patients Treated / Target Enrolment
Phase II Trial of CDK Inhibitor PD 0332991 In Patients with Cancer (Solid tumors: Breast, colon, germ cell, etc.) – included HER2-positive cohort (NCT01037790)	US	Recurrent or metastatic HER2-positive breast cancer RB-positive	Palbociclib + trastuzumab	Schedule 3/1 Palbociclib 125 mg QD + trastuzumab 6mg/kg every 21 days	10/10

Table 1. Ongoing Studies in HER2+ Breast Cancer

Study Title (Tracking No)	Country	Treatment Setting	Regimen	Schedule/ Dosage	Numbers of Patients Treated / Target Enrolment
Phase Ib Study of Palbociclib (PD-0332991) in Combination With T-DM1(Trastuzumab-DM1) (NCT01976169)	US	Recurrent or metastatic HER2-positive breast cancer Must previously treated with trastuzumab	Palbociclib + T-DM1	Schedule 2/1 Palbociclib 150 mg-200 QD Day 5-18 on a 21-day cycle T-DM1 by intravenous infusion at 3.6 mg/kg for 90 minutes on day 1 of each 21 day cycle	9/17
A Phase II study of palbociclib and trastuzumab with or without letrozole in pretreated HER2-positive metastatic breast cancer patients. (SOLTI-13-03; NCT02448420)	Spain	Recurrent or metastatic HER2-positive breast cancer Must previously treated with trastuzumab	Palbociclib + Trastuzumab with or without endocrine therapy	Schedule 2/1 Palbociclib 150 mg-200 QD Trastuzumab 6mg/kg every 21 day	17/45 (Run-in) 107 (expansion)
Neo-Adjuvant Treatment with the CDK4,6 inhibitor Palbociclib in HER2-positive and ER-positive breast cancer: effect on Ki67 and apoptosis before, during and after treatment EudraCT number 2014-001984-11 Acronym: NA-PHER2 (NCT02530424)	Italy	ER+/HER2-positive early stage breast cancer	Trastuzumab+ pertuzumab+ palbociclib + fulvestrant	Trastuzumab 6 mg/kg IV q.3 wks Pertuzumab 840 mg 420 mg IV q. 3 wks Palbociclib 125 mg po q.d. x 21 q. 4 wks Fulvestrant 500mg monthly intra-muscle at the dose of 500 mg every 4 weeks	36/36

1.2.7 Palbociclib Safety Profile

A comprehensive description of Palbociclib Safety Profile is provided in the Palbociclib Investigational Brochure. Data from Phase III studies have demonstrated that palbociclib when given in combination with endocrine therapy is well-tolerated. The primary toxicity of palbociclib is asymptomatic neutropenia which can be effectively managed by dose reduction.

The Safety Profile of Data from the Seminal Phase III studies evaluating the efficacy of palbociclib can be summarized as follows:

The PALOMA-3 phase 3 study [30] enrolled 521 patients with 347 randomized to palbociclib plus fulvestrant and 147 to fulvestrant plus placebo. Neutropenia of all grades was more common in the palbociclib group (81%) than in the control group (3%). Grad 3 and 4 neutropenia were reported in 55% and 10% of patients treated with palbociclib, respectively. Febrile neutropenia was an uncommon event and reported in only 3 patients treated with palbociclib. Grade 3 and 4

leucopenia were reported in 27% and 1% of patients treated with palbociclib, respectively. The following AEs were observed more frequently among patients treated with palbociclib and reported as lower Grade AEs (i.e. Grade 1 or 2) for the majority of patients. Infection (Grade 1-2 40%, Grade 3 2%, Grade 4 <1%); Fatigue (Grade 1-2 37%, Grade 3 2%), Nausea (Grade 1-2 32%); Anemia (Grade 1-2 25%, Grade 3 3%); Thrombocytopenia (Grade 1-2 19%, Grade 3 2%, Grade 4 1%). Alopecia of any grade was reported in 17% of patients in the palbociclib arm. Serious AEs occurred in 13% of patients treated with fulvestrant plus palbociclib. No treatment-related deaths occurred in the study.

The PALOMA-2 phase 3 study [29] enrolled 666 patients with 444 randomized palbociclib plus letrozole and 222 to letrozole plus placebo. Neutropenia of all grades was more common in the palbociclib group (80%) than in the control group (6%). Grad 3 and 4 neutropenia were reported in 56% and 10% of patients treated with palbociclib, respectively. Febrile neutropenia was an uncommon event and reported in only 1.6% patients treated with palbociclib. Grade 3 and 4 leucopenia were reported in 24% and 1% of patients treated with palbociclib, respectively. The following AEs were observed more frequently among patients treated with palbociclib and reported as lower Grade AEs (i.e. Grade 1 or 2) for the majority of patients. Fatigue (Any Grade 37%, Grade 3 2%), Nausea (Any Grade 35%, Grade 3 <1%); Anemia (Any Grade 24%, Grade 3 5%); Thrombocytopenia (Any Grade 16%, Grade 3 1%). Alopecia of any grade was reported in 33% of patients in the palbociclib arm. Serious AEs occurred in 19.6% of patients treated with fulvestrant plus palbociclib. Death due to AEs was reported in 2.3% of patients in the palbociclib arm and 1.8% of patients in the placebo arm.

1.3 Overview of Anti-HER2 Therapies

1.3.1 Trastuzumab

Trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain (ECD) of HER2, thereby inhibiting tumor cell growth and proliferation. The mechanism of action of trastuzumab includes inhibition of ligand-independent receptor dimerization and thereby of downstream signaling transduction pathways (e.g. PI3K signaling). In the advanced-stage setting, trastuzumab-based regimens have improved the survival of patients diagnosed with HER2+ breast cancer, and have favorably changed the dire natural history of advanced HER2+ disease. In the early-stage setting, the addition of trastuzumab to adjuvant chemotherapy has led to a striking reduction in the risk of relapse and death, by 50% and 30%, respectively.

Refer to the Full Prescribing Information for trastuzumab for complete safety information: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

1.3.2 Pertuzumab

Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab augmented anti-tumor activity in HER2-overexpressing xenograft models.

1.4 Overview of Endocrine Therapies

1.4.1 Fulvestrant

Fulvestrant is an ER antagonist approved for the treatment of patients with metastatic ER+ breast cancer. Fulvestrant binds to the ER disrupting the signaling pathway and leading to ER degradation. The recommended dose of fulvestrant is 500mg given by IM injections (two, 250 mg IM injections) on days 1 and 15 of the first month and then monthly thereafter.

Refer to Full Prescribing Information for Fulvestrant for complete safety and dosing information: https://medicalinformation.astrazeneca-us.com/home/prescribing-information/faslodex.html

1.4.2 Aromatase Inhibitors

Refer to Full Prescribing Information for Anastrozole, Letrozole or Exemestane for complete safety information: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
https://www.arimidex.com/prescribing-information.html

2. Study Rationale

Extensive pre-clinical data and initial results from clinical studies point to the added benefit of CDK4/6 inhibition when combined with anti-HER2 therapy (Refer to 1.2.2 and 1.2.6). Data from two randomized phase III studies provide robust evidence of benefit when palbociclib is given in combination with endocrine therapy among patients diagnosed with metastatic ER+ breast cancer.

The current study is designed to evaluate the added benefit of palbociclib when given in combination with anti-HER2 therapy and endocrine therapy. We expect that palbociclib will modulate the endocrine resistance in HER2+ER+ disease and also potentiate the benefits of anti-HER2 therapy.

Cross-talk between HER2 and ER signaling contributes to resistance to endocrine therapy. Breast cancer cell lines that are once sensitive to anti-estrogen therapy become resistant once transfected with the *HER2* gene, suggesting an association between HER-2 overexpression and estrogen independence.

There is a strong link between the actions of estradiol and the G1-S phase transition, where the estradiol effector is the CCND1-CDK4/6-Rb complex. CCND1 is a direct transcriptional target of ER and inhibition of CCND1 halts estrogen-induced S phase entry. Endocrine resistance is associated with persistent CCND1 expression and Rb phosphorylation. Consistent with the notion that the main function of CCND1 is to activate CDK4/6, its oncogenic activity is dependent on CDK4/6-associated kinase activity and CDK4/6 inhibitors are most effective in tumors with gene amplification and overexpression of CCND1 which is common in ER+ breast cancer. A preclinical study evaluating the efficacy of palbociclib in a panel of cell lines showed that palbociclib was most effective for luminal ER+ breast cancer cells, including those that exhibited endocrine resistance [24].

The cross-talk among HER2, steroid hormone signaling, and CDK4/6 role in cell cycle provides a biologic rationale for evaluating the combination of palbociclib with anti-HER2 therapy and anti-hormonal therapy in the clinic [24, 29].

3. Study Design Rationale

3.1 Rationale for Choice of Anti-HER2 and Endocrine Therapy

Targeted anti-HER2 therapy has become the cornerstone of management for patients with advanced HER2-positive breast cancer. Currently, first-line therapy comprises a taxane given in conjunction with trastuzumab and pertuzumab (two anti-HER2 antibodies) [3, 4].

While dual HER2 blockade should be the preferred first line option for the majority of patients, consensus recommendations consider less intense regimens (i.e. trastuzumab-based regimens) for the first-line treatment of HER2+ disease for highly selected patients. (ESO-ESMO 2nd ABC2, NCCN and ASCO guidelines) [31, 32]. Clinicians might consider less intense regimen(s) in the first-line setting particularly for patients with minimal disease burden. Furthermore, the ASCO guidelines also suggest trastuzumab given in combination with chemotherapy as an option for selected patients with HER2+ER+ metastatic breast cancer.

Given the benefits of pertuzumab in the first-line setting, we expect that the majority of patients enrolled in the current study will be treated with a dual anti-HER2 blockade (trastuzumab and pertuzumab). In order to account for potential variability in patterns of use of pertuzumab across different geographic regions, the study allows a non-pertuzumab option (i.e. trastuzumab-based regimen). The non-pertuzumab treatment option is limited to up to 20% of the study population.

In the current study, the choices of endocrine therapy are either an AI (i.e. anastrozole, letrozole or exemestane) or fulvestrant.

Retrospective observations have pointed to the superiority of AI over tamoxifen among patients diagnosed with HER2+ER+ [33]. While the available literature does not provide conclusive evidence to this matter (AI vs. TAM in HER2+ER+) [34], tamoxifen is not considered an endocrine therapy option in the current study. Premenopausal women and men are allowed to participate in the study but premenopausal women must receive ovarian suppression with a LHRH agonist if the patients have not documented ovarian ablation or bilateral oophorectomy or orchiectomy before randomization or during the conduct of the study.

Flexibility in choices of endocrine therapy was deemed critical for the purpose of this clinical study considering patients may have been treated with endocrine agents in the early-stage setting and physicians should be able to choose the endocrine agent deemed appropriate for patients enrolled in the study.

3.2 Rationale for Induction Therapy Prior to Randomization

The current study will enroll patients after completion of pre-specified number of chemotherapy containing anti-HER2 therapy cycles for the treatment of metastatic breast cancer in the first-line setting. Eligible patients are expected to have completed 6 cycles of chemotherapy containing anti-HER2 regimen and a maximum of 8 eight cycles. A minimum of 4 cycles of treatment is acceptable for patients experiencing significant toxicity associated with treatment as long as they are without evidence of disease progression (i.e. CR, PR or SD) by local assessment.

In previous phase III studies (CLEOPATRA and MA 31 study) anti-HER2 blockade (i.e. single or dual anti-HER2 blockade) was given in combination with chemotherapy (i.e. median of six to eight cycles) followed by the continuation of trastuzumab and/or pertuzumab. This is also supported by published treatment guidelines. Based on the available literature, it is expected that the majority of the patients who enter into this study will receive 6-8 cycles of induction therapy.

Eligible patients are expected to have received an optimal anti-HER2 regimen. Clinicians should recommend the combination of trastuzumab, pertuzumab and a taxane for the majority of patients. In order to account for variability in clinical practice and the need for less intense therapeutic regimens for a subset of patients diagnosed with HER2+ER+ disease, clinicians are allowed to recommend the combination of trastuzumab and chemotherapy (defined as a taxane or vinorelbine). The non-pertuzumab treatment option is limited to up to 20% of the study population.

In a previous study, trastuzumab plus vinorelbine showed comparable efficacy to trastuzumab plus docetaxel but with a superior safety profile [35, 36]. The choice of vinorelbine in the current study is limited to the subset of patients treated with trastuzumab-based regimens.

3.3 Rationale for Correlative Science

The pre-clinical and clinical data generated over the past two decades have shed light onto tumor heterogeneity within HER2+ disease. It is clear that HER2+ER+ disease has a unique genomic profile when compared to other disease subtypes. The current study builds upon previous observations and includes a comprehensive molecular characterization of HER2+ER+. This will allow us to answer important translational research questions.

As part of the Primary Translational Research Question, we will compare PFS based upon investigator assessment of progression between patients in the two treatment arms in the subset of patients with tumors bearing a *PIK3CA* mutation. *PIK3CA* genotype will be assessed in circulating tumor DNA (ctDNA).

Constitutive activation of PI3K signaling due to mutation(s) in the PIK3CA gene and/or loss of PTEN, occur in approximately one third of HER2+ breast cancers. Data from recent studies showed that the presence of *PIK3CA* mutation(s) was associated with worse clinical outcome in patients treated with regimens containing trastuzumab and pertuzumab or lapatinib. In the CLEOPATRA study, shorter median PFS was seen among patients with mutant *PIK3CA* tumors. In the control arm of CLEOPATRA, the median PFS arm was 8.6 months for *PIK3CA* mutants versus 13.8 for *PIK3CA* wild type. In the pertuzumab-containing arm of the study, the median PFS arm was 12.5 months for *PIK3CA* mutants versus 21.8 for *PIK3CA* wild type. The impact of *PIK3CA* mutations on patients' outcome could not be attributed to specific mutation, or to mutation(s) in specific exons based on the available dataset.

Data from a recent publication described synergy between HER2 and CDK4/6 inhibitors in cells lines that are either mutant or wild type for *PIK3CA* [27]. Interestingly, the synergistic interaction was strongest in cells with activating *PIK3CA* mutation(s). Furthermore, studies of resistance to endocrine therapy and estrogen-receptor biology suggest the cross talk between PI3K/mTOR/AKT pathway and estrogen pathway could confer the resistance to endocrine therapy. However, recently published data has shown that the degree of improvement of palbociclib in combined with fulvestrant over fulvestrant alone is independent of *PI3KCA* mutational status. There is no difference on PFS or OR between patients with or without

PI3KCA mutation when palbociclib is combined with endocrine therapy [30]. Thus, it is conceivable that *PIK3CA* mutant, HER2+ cancers will be especially susceptible to combined HER2-CDK4/6 blockade, as the increased dependence on the PI3K signaling pathway after CDK4/6 inhibition might be particularly enhanced. If true, this would be particularly important and the absolute benefit with the addition of palbociclib could be greater in the subset of patients with tumors bearing features of PIK3CA activation.

In order to provide a detailed and reliable description of the landscape of the most common somatic mutations (i.e. beyond *PIK3CA*), the current study includes a genomic panel test the results of which may be shared with study investigators. The Oncopanel genomic assay surveys exonic DNA sequences of 447 cancer genes and 191 regions across 60 genes including relevant genes for breast cancer (i.e. *PIK3CA, HER2, ESRI*) to detect somatic mutations, copy number variations and structural variants in tumor DNA extracted from fresh, frozen, or formalin-fixed paraffin-embedded samples.

4. Objectives and Endpoints

4.1 Primary Objectives

The primary objective of this study is to demonstrate that the combination of palbociclib with anti-HER2 therapy plus endocrine therapy is superior to anti-HER2-based therapy plus endocrine therapy in prolonging PFS in participants with hormone receptor-positive, HER2+ metastatic breast cancer who have not received any prior treatment beyond induction treatment in this setting.

4.2 Secondary Objectives

1. To compare measures of tumor control (including OR, CBR, DOR) between the treatment arms
2. To compare median overall survival and overall survival probabilities at 3-years and 5-years between the treatment groups
3. To compare safety and tolerability between the treatment arms
4. To compare the incidence of CNS metastasis between the treatment arms
5. To compare patient reported time to symptom progression as assessed by the FACT-B TOI-PFB.
6. To compare patient reported breast cancer specific health related quality of life (HRQOL) and general health status

4.3 Translational Science Principal Objectives

To compare progression-free survival based upon investigator assessment of progression between patients in the two treatment arms in the subset of patients with tumors bearing a *PIK3CA* mutation. *PIK3CA* genotype will be assessed in circulating tumor DNA (ctDNA).

4.4 Exploratory Objectives

1. To evaluate PFS and OS in genomically-defined breast cancer subgroups based on pre-specified genomic assays
2. To evaluate baseline tumor- and blood-based markers as predictors of benefit from the addition of palbociclib to anti-HER2 therapy plus endocrine therapy
3. To evaluate tumor- and blood-based markers at time of disease recurrence for mechanisms of resistance to therapy

4. To compare serial levels of mutations of circulating tumor DNA (ctDNA) in patients receiving anti-HER2 therapy plus endocrine therapy versus anti-HER2 therapy plus endocrine therapy plus palbociclib
5. To compare mutational profile/copy number variants obtained from tumor tissue to those measured in circulating tumor DNA (ctDNA)
6. To use ctDNA sequencing to compare the inferred tumor transcriptome before and during treatment with anti-HER2 therapy and endocrine therapy with or without palbociclib
7. To determine the trough concentrations of palbociclib when given in combination with trastuzumab plus endocrine therapy or trastuzumab plus pertuzumab plus endocrine therapy
8. To determine trastuzumab and pertuzumab trough concentrations when given in combination with palbociclib plus endocrine therapy
9. To explore correlations between palbociclib exposure and efficacy/safety findings in this patient population
10. To compare the progression-free survival (PFS) outcomes assessed through either local and/or central imaging review with those evaluated using artificial intelligence-based imaging analysis

4.5 Endpoints

4.5.1 Primary

1. Progression-free survival (PFS) as assessed by the Investigator

4.5.2 Secondary

1. Overall Survival (OS)
2. 3-year and 5-year survival probabilities
3. Objective Response (OR: CR or PR)
4. Duration of Response (DOR)
5. Clinical Benefit Rate (CBR: CR or PR or SD ≥ 24 weeks)
6. Incidence of CNS metastasis
7. Safety: Type, incidence, severity (as graded by the NCI CTCAE v. 4.0), seriousness and attribution to the study medications of AEs and any laboratory abnormalities
8. Patient-reported Outcomes: Time to symptom progression (as assessed by the FACT-B TOI-PFB) breast cancer specific health treatment related quality of life and general health status

4.5.3 Correlative

1. Trough plasma concentration of palbociclib, trastuzumab and pertuzumab in the subgroup of patients enrolled in the US.
2. PIK3CA genotype assessed in circulating tumor DNA (ctDNA)
3. Tumor tissue biomarkers including genes, proteins and RNA expression

4.6 Future Biomedical Research

All biospecimens collected for this study will be stored in the Alliance Foundation Biorepository (AFB) until biospecimen accrual and clinical follow up is sufficiently complete to allow for the design and execution of specific correlative analyses.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented patients. The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of disease and/or their therapeutic treatments.

Unless prohibited by local regulations, patients approached to participate in the current study (PATINA/AFT-38) will be asked to indicate on the informed consent forms (ICFs) whether remaining biospecimens and clinical data collected for the PATINA study can be shared with the Mastering Breast Cancer (MBC) Initiative.

The Mastering Breast Cancer Initiative is a multi-institutional, collaborative project aimed at improving outcomes for women with metastatic breast cancer. The overarching purpose of the Mastering Breast Cancer Initiative is to create a mechanism for understanding the natural history of metastatic breast cancer by cataloguing longitudinally studied tumor-specific markers and treatment effects. No additional procedures are included for participants consenting to the Mastering Breast Cancer Initiative. Participation in the Mastering Breast Cancer Initiative allows hosting of limited study tissue and data in the Mastering Breast Cancer Initiative Data and Bio-Repositories upon completion of the PATINA/AFT-38 study. The MBC Data Repository is located at the Mayo Clinic Stats and Data Center and the MBC Biorepository is located at the Alliance Foundation Trials (AFT) Biorepository at Washington University. Both of these repositories will serve as the PATINA study repositories. At the end of the PATINA study, leftover specimens and specific study data will be transferred from the AFT Data and Biorepositories to the MBC Data and Biorepositories at these locations.

The following specimens and study data collected as part of this study (AFT-38/PATINA) during the baseline screening phase from patients consenting to the MBC Initiative will be hosted in the MBC Data and Bio-Repositories:

- Leftover tissue from the archival tissue sample and/or optional tissue from a biopsy of metastatic disease
- Limited baseline clinico-pathologic characteristics, for example: age, disease-free interval, prior treatment for early-stage breast cancer (for complete list of baseline clinico-pathologic characteristics, please refer to Section 10.1)
- Biomarker data (genomic data) from baseline tissue samples

For any patient who consents to the MBC Initiative, this screening data will be available to the MBC Data and Bio-Repositories regardless of whether the patient randomizes into the study or not. Therefore, both for MBC-consented patients who screen fail and for those who randomize, baseline tissue should be submitted to the AFT Biorepository and baseline eCRFs should be completed in the PATINA study database (Medidata RAVE).

In addition to the above baseline data, the following study data collected ***from the patients randomized to the comparator arm (Arm B) only*** who consent to the MBC Initiative will be hosted in the MBC Data and Bio-Repositories:

- Any remaining blood/plasma from germ-line and circulating tumor DNA (ctDNA) collections during treatment phase
- Any remaining tissue from the optional biopsy at disease progression
- Survival data, ongoing treatments, subsequent disease progression data collected in the study database (Medidata RAVE)
- Biomarker data (genomic and/or pathology-based) derived from tumor biospecimens collected from consenting patients at the time of disease progression

5. Study Design

AFT-38 is an international, multicenter, open-label, pivotal Phase III study. The primary objective of this study is to demonstrate that the combination of palbociclib with anti-HER2 therapy plus endocrine therapy is superior to anti-HER2-based therapy plus endocrine therapy in prolonging progression-free survival. The study will enroll 496 patients from approximately 130 sites worldwide.

The study starts after completion of a pre-specified number of chemotherapy containing anti-HER2 therapy cycles for the treatment of metastatic breast cancer in the first-line setting. For the purposes of this study, chemotherapy is defined as either a taxane or vinorelbine (only permitted in patients who receive trastuzumab-based regimen). Eligible participants are expected to have completed 6 cycles of chemotherapy containing anti-HER2-therapy treatment. A minimum of 4 cycles of treatment is acceptable for patients experiencing significant toxicity associated with treatment as long as they are without evidence of disease progression (i.e. CR, PR or SD). The maximum number of cycles is 8. Participants are eligible provided they are without evidence of disease progression by local assessment (i.e. CR, PR or SD).

Eligible participants are expected to have received an optimal anti-HER2 regimen. Clinicians should recommend the combination of trastuzumab, pertuzumab and a taxane for the majority of patients. In order to account for variability in clinical practice and the need for less intense therapeutic regimens for a subset of patients diagnosed with HER2+ER+ disease, clinicians are allowed to recommend the combination of trastuzumab and chemotherapy (defined as a taxane or vinorelbine) prior to the study initiation. Clinicians might also choose a non-pertuzumab option for patients who had been previously treated with pertuzumab in the neo(adjuvant) setting. Eligible participants should continue on the same anti-HER2 regimen initiated prior to study randomization (i.e. trastuzumab and pertuzumab or trastuzumab alone) after randomization. The non-pertuzumab treatment option is limited to up to 20% of the study population. For potentially eligible patients identified during screening who have completed the above required induction treatment, the C1D1 visit must occur within 12 weeks of their last dose of induction therapy.

AFT-38 includes both a Preliminary Screening and a Randomization Screening Phase. Participants potentially eligible to participate on the clinical trial will be consented twice prior to the study randomization – once prior to or during induction therapy to allow for collection of

baseline tissue samples (Pre-Screening Consent) and again prior to randomization to allow for remaining screening tests and study procedures (Main Consent). See Section 10 for more details.

Below lists the biospecimens collected during screening:

Mandatory:

- A representative formalin-fixed paraffin embedded (FFPE) archival (primary breast or metastatic) tumor tissue block (preferred) or at least 15 unstained slides from such a block, along with a pathology report documenting HER2 positivity and hormone receptor positivity

Optional:

- Research biopsy: A biospecimen from *a* metastatic site if clinically feasible ***or***
- Tissue sample from recently biopsied metastatic site

Below lists the biospecimens collected during the study:

Mandatory:

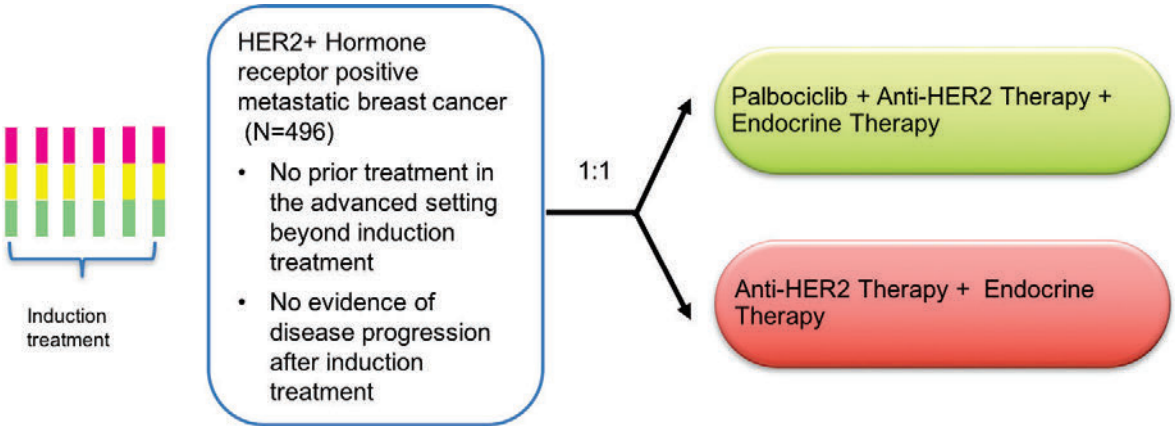
- Blood draw for germ-line DNA at two timepoints (C1D1 and C4D1)
- Blood draw for circulating tumor DNA (ctDNA) at three timepoints (C1D1, C4D1 and end of treatment)

Optional:

- Biopsy of metastatic site at disease progression ***or***
- Tissue sample from recently biopsied metastatic site at disease progression

For more details, please see PATINA (AFT-38) Correlative Science Manual (CSM), on the BioMS website, which is accessible via the AFT portal, https://alliancefoundationtrials.org

Figure 1. Study Schema



Arm A: Palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle, in addition to standard anti-HER2 therapy and standard endocrine therapy

Arm B: Standard anti-HER2 therapy and endocrine therapy
Endocrine Therapy: AI of choice or Fulvestrant. Premenopausal women must receive ovarian suppression with a LHRH agonist if the patients have not documented ovarian ablation or bilateral oophorectomy before randomization or during the conduct of the study

6. Patient Selection/Population

AFT does not grant eligibility waivers. Investigators must carefully consider any condition that in the opinion of the investigator would interfere with participation in the study. Please contact the study chair for eligibility questions.

6.1 Inclusion Criteria (Preliminary Screening)

1) Signed Preliminary Informed Consent Form obtained prior to any study specific assessments and procedures
2) Age ≥18 years (or per national guidelines)
3) Participants must have histologically confirmed invasive breast cancer that is metastatic or not amenable for resection or radiation therapy with curative intent. Histological documentation of metastatic/recurrent breast cancer is not required if there is unequivocal evidence for recurrence of the breast cancer.
4) Patients must have histologically confirmed HER2+ and hormone receptor positive (ER+ and/or PR+), metastatic breast cancer. ER, PR and HER2 measurements should be performed according to institutional guidelines, in a CLIA-approved setting in the US or certified laboratories for Non-US regions. Cut-off values for positive/negative staining should be in accordance with current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines.
5) Patients must agree to provide a representative formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) from primary breast or metastatic site (archival) *OR* at least 15 unstained slides from such a block, along with a pathology report documenting HER2 positivity and hormone receptor positivity.
6) Patients should be willing to provide a representative tumor specimen obtained from recently biopsied metastatic disease if clinically feasible. This is recommended but optional tissue.

6.2 Inclusion Criteria (Randomization Screening)

7) Signed Main Informed Consent Form obtained prior to any study specific assessments and procedures
8) Age ≥18 years (or per national guidelines)
9) ECOG performance status 0-1
10) Patients must be able and willing to swallow and retain oral medication without a condition that would interfere with enteric absorption.
11) Serum or urine pregnancy test must be negative within 7 days of randomization in women of childbearing potential. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation. Women of childbearing potential and male patients randomized into the study must use adequate contraception for the duration of protocol treatment which is for 6 months after the last treatment with palbociclib if they are in Arm A and for 7 months

after last treatment with trastuzumab if in either Arm A or Arm B. Adequate contraception is defined as one highly effective form (i.e. abstinence, (fe)male sterilization OR two effective forms (e.g. non-hormonal IUD and condom / occlusive cap with spermicidal foam / gel / film / cream / suppository).

12) Resolution of all acute toxic effects of prior induction anti-HER2-based chemotherapy regimen to NCI CTCAE version 4.0 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion) 12 weeks between last dose of chemotherapy–anti-HER2 therapy and randomization are allowed. Endocrine therapy could start before study randomization.
13) Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

Prior Treatment Specifics

14) Patients may or may not have received neo/adjuvant therapy, but must have a disease-free interval from completion of anti-HER2 therapy to metastatic diagnosis ≥6 months.
15) Patients must have received an acceptable, standard, chemotherapy containing anti-HER2 based induction therapy for the treatment of metastatic breast cancer prior to study enrollment. For this study, chemotherapy is limited to a taxane or vinorelbine (only for trastuzumab-based regimen). Eligible patients are expected to have completed 6 cycles of chemotherapy containing anti-HER2-therapy treatment. A minimum of 4 cycles of treatment is acceptable for patients experiencing significant toxicity associated with treatment as long as they are without evidence of disease progression (i.e. CR, PR or SD). The maximum number of cycles is 8. Patients can randomize immediately following completion of their induction therapy, or for those who have already completed induction, a gap of 12 weeks between their last infusion/dose of induction therapy and the C1D1 visit is permitted. Patients are eligible provided they are without evidence of disease progression by local assessment (i.e. CR, PR or SD).
16) Patients with a history or presence of asymptomatic CNS metastases are eligible provided they meet all of the following criteria:
    - Disease outside the CNS is present.
    - No evidence of interim progression between the completion of induction therapy and the screening radiographic study
    - No history of intracranial hemorrhage or spinal cord hemorrhage
    - Not requiring anti-convulsants for symptomatic control
    - Minimum of 3 weeks between completion of CNS radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade ≥ 3) acute toxicity with no ongoing requirement for corticosteroid

Baseline Body Function Specifics

17) Absolute neutrophil count ≥ 1,000/mm3
18) Platelets ≥ 100,000/mm3
19) Hemoglobin ≥ 10g/dL
20) Total serum bilirubin ≤ ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert’s Syndrome.
21) Aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) ≤ 3 × institutional ULN (≤5 x ULN if liver metastases are present).

22) Serum creatinine below the upper limit of normal (ULN) of the institutional normal range or creatinine clearance ≥ 60 mL/min/1.73 m2 for patients with serum creatinine levels above institutional ULN.
23) Left ventricular ejection fraction (LVEF) ≥ 50% at baseline as determined by either ECHO or MUGA

6.3 Exclusion Criteria (Randomization)

1) Concurrent therapy with other Investigational Products.
2) Prior therapy with any CDK 4/6 inhibitor.
3) History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib.
4) Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A isoenzymes within 7 days of randomization (see Section 8.6.3 for list of strong inhibitors or inducers of CYP3A isoenzymes).
5) Uncontrolled current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, or psychiatric illness/social situations that would limit compliance with study requirements. Ability to comply with study requirements is to be assessed by each investigator at the time of screening for study participation.
6) Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to randomization, irrespective of the method of contraception used, are excluded from this study because the effect of palbociclib on a developing fetus is unknown. Breastfeeding must be discontinued prior to study entry.
7) Patients on combination antiretroviral therapy, i.e. those who are HIV-positive, are ineligible because of the potential for pharmacokinetic interactions or increased immunosuppression with palbociclib.
8) QTc interval >480 msec, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes.
9) Patients with clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis

7. Method of Treatment Assignment

7.1 Site Enrollment/Randomization Requirements

Site must submit all required essential documents including, but not limited to:

- IRB/Regulatory Approval
- Clinical Study Agreement
- Investigator 1572
- Institutional informed consent forms
- System training and access for all required staff
- Protocol and Good Clinical Practice training for all required staff
- Documentation of Site Initiation Visit

Essential documents must be submitted to the AFT (IQVIA) electronic Trial Master File, accessible via the AFT portal: https://alliancefoundationtrials.org.

7.2 Patient Randomization and Allocation to Treatment:

Patient randomization and enrollment into the study will be facilitated using the Oracle web-based IRT (interactive response technology) system, accessible via the AFT portal: https://alliancefoundationtrials.org.

Patients must sign informed consent prior to any screening or study-related testing, including submission of biospecimens. After the signed Preliminary Screening Informed Consent Form has been obtained, the study site will register the patient in the IRT system to obtain a unique patient identification number which will stay the same throughout the entire study. After the Main Informed Consent Form is signed, all eligibility requirements for enrollment have been met and the required tissue specimen has been submitted to the central biorepository/lab, patients may be enrolled/randomized in the IRT system. The time window from signing the Main Consent to completion of all randomization assessments is 28 days. Results of screening tests performed prior to obtaining Main Informed Consent and within 42 days of randomization may be used rather than repeating required tests. (This does not apply to the baseline tumor assessments which must be done within 28 days of randomization).

Patients screened but not randomized for any reason must be registered as a Screening Failure in IRT.

Following randomization, the IRT system will provide the site with a printable confirmation of enrollment and treatment randomization information. Please print this confirmation for your records. The site will receive information regarding dispensation of drug and maintenance of adequate drug supply via IRT, upon randomization.

7.3 Stratification Factors

Randomization will be stratified by pertuzumab use (yes vs. no), by prior anti-HER2 therapy in the (neo) adjuvant setting (yes vs. no), by type of endocrine therapy (AI or fulvestrant), and by best response to induction therapy (CR or PR vs. SD) determined by investigator assessment.

Eligible participants should continue on the same anti-HER2 regimen initiated prior to study randomization (i.e. trastuzumab and pertuzumab or trastuzumab alone) after randomization. The non-pertuzumab treatment option is limited to up to 20% of the study population.

7.4 Treatment Assignment

IP Treatment is comprised of palbociclib treatment for patients randomized into Arm A.

Non-IP Treatment is comprised of standard anti-HER2 therapy (trastuzumab and/or pertuzumab) and endocrine therapy (AI or fulvestrant) for patients randomized into Arm A and B.

Palbociclib is the only investigational product (IP) of this trial and will be provided free of charge by the Sponsors. Endocrine therapy and anti-HER2 therapy will not be provided by the Sponsors and must be selected by the Investigator as part of a standard of care therapy.

8. Treatment Plan

During this phase, patients randomized into Arm A will receive IP treatment (palbociclib) and Non-IP treatment (anti-HER2 therapy plus endocrine therapy) and patients randomized into Arm B will receive Non-IP treatment only (anti-HER2 therapy plus endocrine therapy).

Cycle 1 Day 1 (C1D1) should occur within 14 days of randomizing the patient. Sites should try to schedule the C1D1 visit to coincide with the patient's next anti-HER2 infusions which are administered on an every 3-week cycle, in order to reduce the burden to the patient of multiple visits.

Patients will continue with the Treatment Phase until they meet the criteria for Clinical Follow-up or Survival Follow-up as outlined below:

1) Clinical Follow-up Phase: Patient begins this phase when/if IP therapy (Arm A) and Non-IP therapy is permanently discontinued due to non-PFS event reason. This phase includes all of the visits required by the Schedule of Assessments through disease progression. Types of delays or interruptions in IP dosing which will not trigger discontinuation of IP treatment are specified in Section 9.

2) Survival Follow-up Phase: Patients who discontinue Study Treatment due to a disease progression will move to the Survival Follow-up Phase.

3) Randomized patients on either Arm who are deemed ineligible prior to first dose, or refuse to start their initial treatment will move to the Survival Follow-up Phase.

8.1 Palbociclib – Investigational Product (IP)

8.1.1 Palbociclib Administration

Palbociclib should be taken orally, once per day with food around the same time, starting at the 125-mg dose. Treatment is continuous daily for 21 days, followed by 7 days off, to complete a 28-day cycle.

Expected toxicities and potential risks as well as allowable dose modifications are described in section 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy within the Treatment Phase.

Administration is performed on an outpatient, self-administration basis. On days when a patient is scheduled for a clinic visit (dispensing visit), the patient should take the scheduled palbociclib dose once the visit assessments for potential hematologic and non-hematologic toxicities (see Section 9.1.2) have been performed and are within acceptable range unless otherwise indicated.

Missed doses of palbociclib (meaning doses that are missed for one day) should not be made up. For example, if a dose is entirely missed for one day, dose should be skipped and NOT retaken the next day; patients should resume regular dosing as prescribed the following day. If a dose is vomited at any time after taking palbociclib, a replacement dose should NOT be taken.

Patients who inadvertently take 1 extra dose during a day must skip the next day's dose and notify his or her treating physician. If a patient takes more than two doses of palbociclib in a day, the patient should bring this to the attention of his or her treating physician.

Patients should be instructed to record daily administration of the study drugs in a drug or medication diary.

8.1.2 Formulation, Packaging and Labeling

Palbociclib Drug Substance and Drug Product are manufactured, labelled and packed according to current Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines for use in the clinical studies. Each lot of palbociclib for clinical studies is subjected to a series of quality control tests to confirm its identity, purity, potency, and quality.

Palbociclib will be manufactured by Pfizer and provided by the study Sponsor as capsules or tablets containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. Palbociclib capsules supplied to sites will be in High Density Polyethylene (HDPE) bottles containing 75 mg, 100 mg, or 125 mg capsules and are labeled for clinical use. The capsules can be differentiated by their size and color (see below).

Table 2: Palbociclib Capsule Characteristics

Dosage	Capsule color	Capsule size
75 mg	Sunset Yellow	2
100 mg	Caramel/Sunset Yellow	1
125 mg	Caramel	0

Palbociclib tablets supplied to sites will be in foil/foil blisters containing 75 mg, 100 mg, or 125 mg tablets and are labeled for clinical use. The tablets can be differentiated by their shape and color (see below).

Table 3: Palbociclib Tablet Characteristics

Dosage	Tablet color	Tablet Shape
75 mg	Lavender	round
100 mg	Light Green	oval
125 mg	Lavender	oval

8.1.3 Storage, Handling and Processing

Palbociclib capsules and tablets should be stored at controlled and monitored room temperature specified on the product labels. Further storage and stability conditions are stated in the palbociclib IB. Investigators and site staff are requested to check storage temperatures daily (i.e. manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products.

Deviations from the storage requirements, including any actions taken, must be documented and reported to AFT. Once a deviation is identified, palbociclib must be quarantined and not used until receipt of documentation of permission to use the investigational product.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Medication which has been returned by the patients should be stored separately from medication that needs to be dispensed.

8.1.4 Dispensation and Accountability

The study IRT system will be used by clinical sites to acknowledge receipt of study drug. Damaged shipments will be replaced.

The patient number should be recorded on the container label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit and should further be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Only a single capsule or tablet strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously received and unused medication to the site and new capsules will be dispensed.

To ensure adequate records and patient compliance monitoring, study medication will be accounted for by the site on a Drug Accountability Log. Hence, the site must maintain a careful record of the inventory and disposition of the agent. Accurate records of all IP received at, dispensed to, returned from, returned to, and disposed of by the study site should be recorded as instructed by the study sponsor.

Patients will be instructed to return previously dispensed containers (including unused drug and/or empty bottles/blisters) as well as their completed palbociclib Drug Diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit. Unused returned medication MUST NOT be re-dispensed to patients. The number of remaining capsules/tablets will be documented and recorded on the Drug Accountability Log and within the eCRF. Drug accountability for palbociclib will be performed at each study visit prior to dispensing drug supply for the next cycle(s).

8.1.5 Destruction and Return

Sites will have to destroy or return unused investigational product(s). The site's principal investigator must ensure that any materials are destroyed or returned in compliance with applicable environmental local regulations, institutional policy, and any special instructions provided by the study Sponsor. The site's method of IP destruction must be agreed to by the Sponsor in writing. Ideally, verification of drug accountability by the monitor should be

completed before any IP is destroyed at site. However, in instances when IP needs to be destroyed prior to a monitor visit (for example, due to limited storage capacity), instructions provided to all sites by the sponsor (Drug Destruction Prior to CRA Review) must be followed. In all cases, destruction or return of investigational product must be adequately documented.

8.2 Endocrine Therapy – Non-Investigational Product (Non-IP)

Endocrine treatment may have already started before the patient enters the study.

The following standard endocrine treatment agents (also referred to as background treatment) are allowed for Arm A and Arm B:

- Non-steroidal AIs (anastrozole, letrozole) for postmenopausal women.
- Steroidal AI (exemestane) for postmenopausal women.
- Fulvestrant for postmenopausal women
- LHRH agonists in combination with AI or fulvestrant for premenopausal women
- Surgical or radiologic ablation of the ovaries is also allowed, but additional endocrine treatment has to be given to these patients.

Locally obtained commercial supply of anastrozole, letrozole, exemestane, fulvestrant or LHRH agonists will be administered to the patients at the discretion of the principal investigator (or his/her designee) as well as according to standard institutional or regional practice. Generics are allowed, if locally available.

Administration is performed on an outpatient, self-administration basis according to local requirements and local standard practice.

Recommended dosing regimens of oral endocrine therapy are:

- Letrozole: 2.5 mg orally, once a day
- Anastrozole: 1 mg orally, once a day
- Exemestane: 25 mg orally, once a day
- Fulvestrant: 2 x 250mg injections on D1 and D15 of Cycle 1 and q 4 weeks thereafter

Injection of LHRH agonist is mandatory for premenopausal women. If a premenopausal woman is receiving LHRH agonist in combination with AI or fulvestrant, it is recommended that she receives monthly injections rather than every-3-month depot injections.

Specific storage conditions, handling, dispensation and administration instructions have to be followed according to local regulations and in accordance with respective local package inserts and/ or for sites outside of the US, local Summary of Product Characteristics (SmPCs) information.

Expected toxicities and potential risks can be obtained from respective local pack inserts and or local SmPCs.

Missed doses of endocrine therapy should not be made up. If a patient encounters difficulty tolerating endocrine therapy, the treating provider should make all possible efforts to continue the patient on adjuvant endocrine therapy, including the use of short drug holidays and rotation among endocrine agents, while continuing treatment with palbociclib. If the patient is on Arm A and despite best efforts is unable to tolerate endocrine medication altogether, palbociclib and anti-HER2 therapy must continue. If palbociclib is stopped for a patient on Arm A due to reasons other than PFS event, it is strongly recommended that the patient resume endocrine therapy once symptoms resolve, or change to alternative endocrine therapy. See Section 12 for the schedule of assessments and follow-up.

8.3 Trastuzumab – Non-Investigational Product (Non-IP)

8.3.1 Description, Form, and Prescription

This study will use trastuzumab from commercial supply. If the patient has known hypersensitivity to benzyl alcohol, trastuzumab must be reconstituted with sterile water for injection (SWFI). Trastuzumab that has been reconstituted with SWFI must be used immediately and any unused portion discarded. Use of other reconstitution diluents should be avoided. Determine the dose of trastuzumab needed based upon guidance provided in the latest package insert for q3w dosing schedules.

8.3.2 Administration

Trastuzumab infusion should be performed according to local guidelines.
Dosing begins on Day 1 of Cycle 1 and continues at every three-week intervals throughout the study.

Patients should continue on the same dose they were given during induction unless there was a break from last dose of induction therapy to the C1D1 visit date necessitating a re-loading dose (per protocol, a break of up to 12 weeks is permitted). Consult the latest package insert for guidance regarding re-loading dose requirements.

The use of subcutaneous formulation of trastuzumab is optional where available. If administered, local guidelines should be followed.

8.3.3 Ordering

Trastuzumab is a commercially available agent and therefore ordering should be performed as standard policy at the investigational site.

8.3.4 Drug Supplies and Accountability

Trastuzumab is a commercially available agent and therefore accountability should be performed as standard policy at the investigational site.

Expected toxicities and potential risks can be obtained from respective local pack inserts and or local SmPCs.

8.4 Pertuzumab – Non-Investigational Product (Non-IP)

8.4.1 Description, Form and Preparation

This study will use pertuzumab from commercial supply. Pertuzumab drug product is provided as a single use formulation containing 30 mg/mL pertuzumab in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20. Each 20 mL vial contains 420 mg of pertuzumab (14.0 mL/vial). Dextrose 5% solution should not be used. The preparation of pertuzumab solution should follow the manufacturer recommendations.

Expected toxicities and potential risks can be obtained from respective local pack inserts and or local SmPCs.

8.4.2 Administration

Pertuzumab infusion should be performed according to local guidelines. Patients should be observed for fever and chills or other infusion-associated symptoms.

Dosing should begin on Day 1 of Cycle 1 (C1D1) and continue at every three-week intervals throughout the study, following the dosing instructions provided in the latest pertuzumab package insert. For patients who have experienced a gap between their last pertuzumab dose and the C1D1 visit, consult the latest pertuzumab package insert for re-loading dose requirements.

The use of subcutaneous formulation of pertuzumab is optional where available. If administered, local guidelines should be followed.

8.4.3 Ordering

Pertuzumab is a commercially available agent and therefore ordering should be performed as standard policy at the investigational site.

8.4.4 Drug Supplies and Accountability

Pertuzumab is a commercially available agent and therefore accountability should be performed as standard policy at the investigational site.

Expected toxicities and potential risks can be obtained from respective local package inserts and or local SmPCs.

8.5 Pre-Treatment Criteria

8.5.1 Cycle 1 Day 1

Patients must meet baseline body function specifics listed in Section 5.1 Inclusion Criteria above.

8.5.2 Subsequent Cycles

Retreatment with palbociclib at the start of a new cycle that requires a clinic visit may not occur until all of the following parameters have been met:

- Platelet count ≥ 75,000/mm3;

- ANC ≥ 1000/mm3 and no fever;
- See Section 9.1 for additional retreatment information

8.6 Concomitant Medications

All prior treatment or medication administered during the 30 days prior to randomization and any concomitant therapy administered to the patient throughout the study until 42 days after confirmation of disease progression/end of treatment must be recorded in the Medidata RAVE EDC system on the respective page of the eCRF. The generic or trade name of the drug must be specified along with the dose, the duration of treatment, relation to AE and indication for use.

8.6.1 Permitted Ancillary Medications

Supportive care medications are allowed at any time on trial, as long as they are not included in the list of prohibited medications based on CYP induction (see Section 8.6.3).

Specifically, the following agents are permitted:

- Antiemetics
- Antidiarrheal therapy
- Antiallergic measures such as corticosteroids and antihistamines
- Bisphosphonates
- Denosumab
- Agents to assist in management of endocrine therapy-induced side effects (Nonsteroidal anti-inflammatory drugs [NSAIDs], gabapentin, duloxetine, venlafaxine, etc.).
- Diabetes management medication including metformin
- Rank Ligand Inhibitors

8.6.2 Prohibited Concomitant Medications

Growth factors, including Granulocyte Colony Stimulating Factor (G-CSF), are not allowed on this trial (with the exception of situations where a patient becomes clinically and medically unstable due to neutropenia).

8.6.3 CYP3A Inhibitors/Inducers

Strong CYP3A inhibitors/inducers: Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are strong CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans. The concurrent use of the following compounds is not allowed in the study and should be discontinued within 7 days prior to randomization:

- Strong CYP3A inducers, including carbamazepine, phenytoin, primidone, rifampin, rifapentin, and St. John's wort.
- Strong CYP3A inhibitors, including, boceprevir, clarithromycin, conivaptan, delavirdine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit.

The following compounds are not allowed 7 days prior to the PK sampling days until the completion of the PK samples collection in each period:

- Moderate CYP3A inhibitors including amprenavir, atazanavir, diltiazem, erythromycin, fosamprenavir, verapamil.
- Moderate CYP3A inducers including felbamate, nevirapine, phenobarbital, rifabutin.

8.6.4 Anticancer Therapies

No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, radiation therapy or endocrine therapy other than those allowed in the protocol will be permitted during the active Treatment Phase. In general, any drugs containing "for the treatment of breast cancer" on the product label are not permitted during Treatment Phase of the study.

8.6.5 Antacid Agents

The concomitant use of Proton-pump inhibitors (PPI) with palbociclib is prohibited 7 days prior to the PK sampling days until the completion of the PK samples collection in each period.

8.6.6 Medications Not Recommended

The following treatments are not recommended throughout the duration of the Treatment Phase. Alternative therapies should be considered whenever possible:

- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids are allowed.
- The use of herbal medicine is not recommended during the Treatment Phase.
- CYP3A Substrates with a Narrow Therapeutic Index: The dose of the sensitive CYP3A4 substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced when given concurrently with palbociclib as palbociclib may increase their exposure.

8.6.7 Concomitant Radiotherapy or Surgery

Any concurrent radiotherapy (except palliative radiotherapy as specified below) is prohibited throughout the duration of the active Treatment Phase of the study.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression.

In view of the current lack of data about the interaction of palbociclib with radiotherapy, palbociclib treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming 1 week after. For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (e.g., lesions at risk for spontaneous micro-fractures or painful lesions). The dates on which palliative radiotherapy is administered should be recorded on the appropriate CRFs. Patients may continue

endocrine therapy and anti-HER2 therapy during the course of palliative radiotherapy at the discretion of the treating physician.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and palbociclib required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping palbociclib is recommended at least 7 days prior to elective surgery. Postoperatively, the decision to reinitiate palbociclib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery. Patients can continue endocrine and/or anti-HER2 therapy if palbociclib is held for surgery.

9. Dose Modifications/Toxicity Management

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of palbociclib may need to be adjusted. No dose reduction for trastuzumab, pertuzumab and endocrine therapy is permitted, but dose interruptions are allowed.

Incidence, nature, and severity of AEs triggering dose or study treatment modifications are to be assessed by the investigator and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0) as AE related dose and treatment modification recommendations are based on this grading scale.

9.1 Palbociclib

9.1.1 Dose Modifications/Toxicity Management

Dose or treatment modifications for palbociclib are allowable and may occur as dose interruptions (within a cycle), dose delays (between cycles) or dose reductions.

In the event of significant palbociclib treatment-related toxicity, palbociclib dosing may be interrupted or delayed or reduced as described below.

In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

The start of a cycle is defined as the day when palbociclib administration begins, starting with the first palbociclib dose at baseline (Cycle 1, Day 1). In case of palbociclib dose delays, administration of endocrine therapy and anti-HER2 therapy will continue according to the pre-planned schedule.

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions Section (Section 9.1.4) unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied, the patient may need to return to the clinic to receive new drug supply.

9.1.2 Palbociclib Dosing Interruptions/Delays

In general, cycles should be 28 days long unless the start of a new cycle is delayed.

Doses missed within a cycle (meaning dose interruptions) are not made up. If, e.g. 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 cycle should be delayed according to guidelines within this section, if an AE requiring a dose hold has not returned to baseline or grade 2 level by Day 1 of the next planned cycle with the exception of alopecia.

Patients experiencing one or more of the following AEs should have their palbociclib treatment interrupted/delayed until criteria for retreatment.

The following AEs need to return to baseline or grade 2 level by Day 1 of the next cycle:

- Uncomplicated Grade 3 or 4 neutropenia (Absolute Neutrophil Count (ANC) < 1000/mm3)
- Grade 3 or 4 neutropenia (ANC < 1000/mm3) associated with a documented infection or fever ≥ 38.3°C, 101°F (febrile neutropenia)
- Grade 3 or 4 thrombocytopenia (Platelet count < 50,000/mm3)
- Grade ≥ 3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)

The following needs to return to baseline or grade 1 level by Day 1 of the next cycle:

- Grade 2 or 3 non-hematologic toxicity persisting despite optimal medical treatment, lasting more than 3 weeks, and unacceptable to patient and/or provider.

In case of concurrent occurrence of >3x ULN ALT or AST and >2x ULN total bilirubin at any time during the trial, **palbociclib will be permanently discontinued**.

It is also important to monitor patients for pulmonary symptoms indicative of interstitial lung disease (ILD)/pneumonitis (e.g. hypoxia, cough, dyspneoa). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt palbociclib immediately and evaluate the patient. **Permanently discontinue palbociclib** in patients with severe ILD or pneumonitis.

9.1.3 Palbociclib Retreatment Criteria

In the case of a treatment interruption or delay, retreatment with palbociclib may not occur until all of the following parameters have been met:

- Platelet count ≥ 75,000/mm3;
- ANC ≥ 1000/mm3 and no fever;

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be adjusted as clinically indicated.

If the retreatment parameters are met within 4 weeks of treatment interruption or cycle delay, palbociclib may be resumed.

If these parameters have not been met after 4 weeks of dose interruption (including the scheduled 1 week off treatment) or cycle delay, the patient should permanently discontinue palbociclib treatment.

9.1.4 Palbociclib Dose Reductions

The palbociclib dose may need to be reduced, following a dose interruption or cycle delay when treatment is resumed.

- No specific dose adjustments are recommended for Grade 1 or short lasting Grade 2 (< 4 weeks) treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances and document the changes in the CRF.
- For palbociclib related, Grade 2 toxicity lasting for ≥ 4 weeks (excluding alopecia) or for palbociclib related Grade 3 toxicities (despite maximum supportive care as judged by the investigator), palbociclib dose reduction is recommended for all subsequent cycles. Taking palbociclib according to recommendation (i.e., with food) should be reinforced and confirmed. Dose reduction of palbociclib by one dose level, and, if needed, by two dose levels (Table 3) may be required depending on type and severity of the toxicity encountered. Once a dose has been reduced for a given patient, all subsequent cycles should generally be administered at that dose level, unless further dose reduction is required. Dose re-escalation of palbociclib from 100mg to 125 mg is not allowed. Cautious dose re-escalation from 75mg to 100mg can be considered per investigator discretion. Patients requiring more than 2 dose reductions will discontinue palbociclib treatment permanently. If the patient remains on anti-HER2 and/or endocrine therapy(ies), they remain in the Treatment Phase. If all study medications are discontinued (for reasons other than disease progression), the patient should switch to the Clinical Follow-up Phase (see Section 10.4.2).

Table 3: *Palbociclib Dose Levels and Dose Reduction Schedule*

Dose Level	**Palbociclib once daily on days 1-21, followed by 7 days off**
Starting dose	125 mg/d
Level -1 (first dose reduction)	100 mg/d
Level -2 (second dose reduction)	75 mg/d
Discontinue palbociclib treatment	

9.1.5 Dose Modifications/Toxicity Management – Endocrine Therapy

Patients should not hold or discontinue endocrine therapy for side effects potentially or likely related to concomitant anti-HER2 therapy and/or palbociclib as per the investigator's judgment. If a patient finds oneself not able to tolerate endocrine therapy, an attempt to change to an alternative endocrine therapy is a priority, while continuing treatment with anti-HER2 therapy and/or palbociclib. If a patient is considering stopping endocrine medication altogether, palbociclib and anti-HER2 therapy must continue.

9.1.6 Dose Modifications/Toxicity Management – Anti-HER2 Therapy

In general, patients should not hold or discontinue anti-HER2 therapy for side effects potentially or likely related to concomitant palbociclib as per the investigator's judgment. If anti-HER2 therapy is discontinued, patients may continue on endocrine therapy and/or palbociclib as per the investigator's judgment. Please see Table 4 for palbociclib-related AEs that may necessitate anti-HER2 therapy holds/discontinuations (if determined by investigator to be also related to the anti-HER2 therapies).

All patients will undergo scheduled LVEF assessments by ECHO or MUGA scans. The results of the LVEF assessments will be used to determine if trastuzumab and pertuzumab administration can be continued. Refer to Figure 2 for the algorithm for continuation and discontinuation of study treatment on the basis of asymptomatic LVEF assessment.

Diarrhea and rash are considered EGFR-related risks based on the mechanism of action of pertuzumab. To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication should be considered, and patients should be treated with fluids and electrolyte replacement, as clinically indicated. Treatment recommendations for EGFR-associated rash include topical or oral antibiotics, topical pimecrolimus, and topical or (for severe reactions) systemic steroids. These agents may be used in patients experiencing pertuzumab-related rash, as clinically indicated.

During study treatment, some toxicity may be attributable to palbociclib, trastuzumab, or pertuzumab. It is important to evaluate the possible cause of toxicity and weigh risk versus benefit for each agent to determine the schema of dose modifications (e.g., which agent to prioritize for maintaining dose level and the sequence of dose modifications).

General guidelines are provided in the following subsections based on the known safety profile of study drugs.

Table 4: *AE-triggered Dose Modifications and Treatment Management for Palbociclib, with Trastuzumab, and Pertuzumab Adjustments as necessary (if AEs deemed also related to the anti-HER2 therapies, per investigator judgment)*

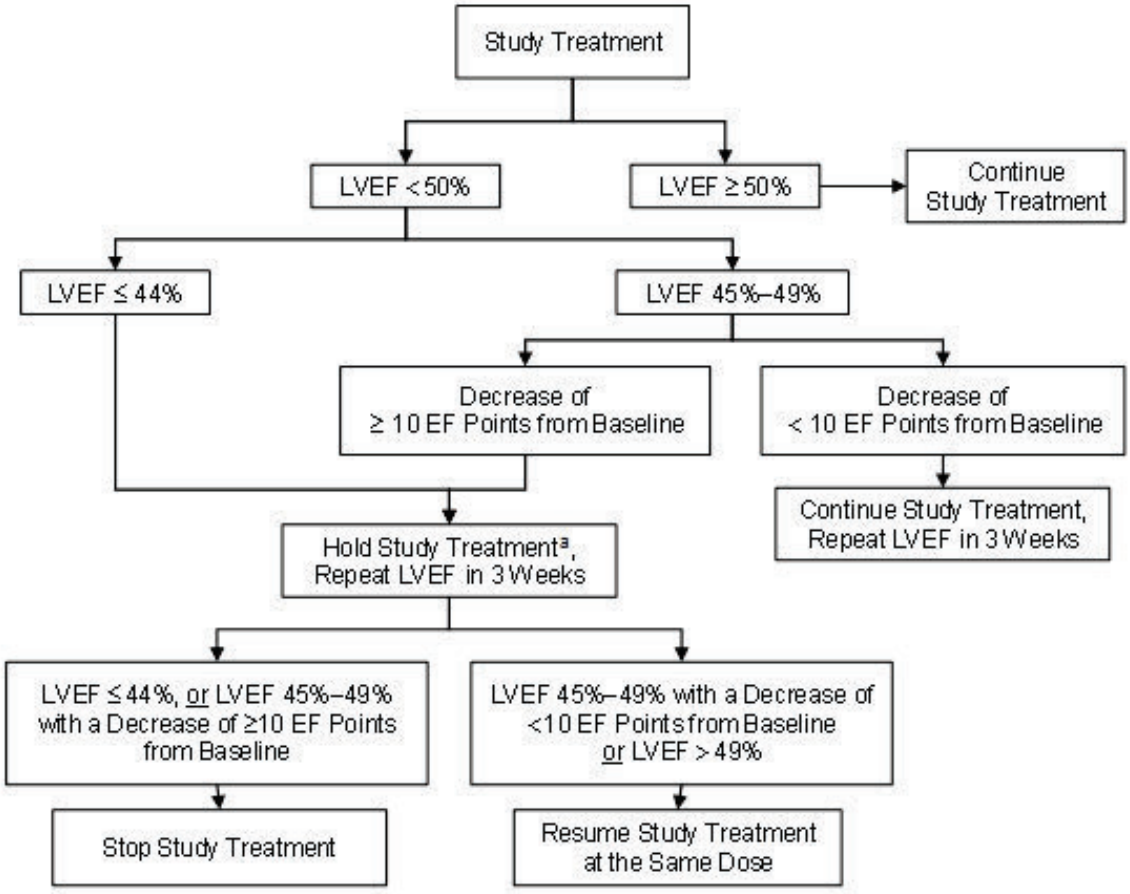
CTCAE v.4.0 Adverse Event	CTCAE Grade	Intervention
Febrile Neutropenia	3, 4	Hold palbociclib until clinically stable, if ANC recovers (ANC ≥ 1000mm3) and absence of fever, then 1st appearance: Resume at next lower dose 2nd appearance: Resume at next lower dose ≥3rd appearance: Discontinue Hold trastuzumab and pertuzumab until clinically stable. If ANC recovers (ANC ≥ 1000mm3) resume treatment without dose reduction. Pertuzumab may be discontinued in case of repeat grade 3 or 4 neutropenic fever (≥ 1 episode)
Neutrophil count decreased (Note: The use of growth factors is not recommended)	3	Hold palbociclib until ≥ 1000/mm3, then 1st appearance: Resume at same dose level 2nd appearance: Resume at next lower dose 3rd appearance: Resume at next lower dose Hold pertuzumab until ≥ 1000/mm3. Resume treatment without dose reduction
	4	Hold until ≥ 1000/mm3, then 1st appearance: Resume at next lower dose 2nd appearance: Resume at next lower dose ≥3rd appearance: Discontinue Hold pertuzumab until ≥ 1000/mm3. Resume treatment without dose reduction
Platelet count decreased	3	Hold palbociclib until ≥ 75000/mm3, then 1st appearance: Maintain dose 2nd appearance: Resume at next lower dose 3rd appearance: Resume at next lower dose
	4	Hold palbociclib until ≥ 75000/mm3, then 1st appearance: Resume at next lower dose 2nd appearance: Resume at next lower dose ≥3rd appearance: Discontinue
Anemia	3, 4	Reduce palbociclib to next lower dose only in cases of protracted symptomatic anemia considered to be related to palbociclib

CTCAE v.4.0 Adverse Event	CTCAE Grade	Intervention
ALT increased with total bilirubin < 2X ULN (in the absence of cholestasis or hemolysis)	3	Hold palbociclib until clinically stable and recovered to ≤ Grade 1 or to baseline, then 1st appearance: Resume at same dose 2nd appearance: Resume at next lower dose ≥3rd appearance: Discontinue Hold pertuzumab until clinically stable and recovered to ≤ Grade 1 or to baseline, then 1st appearance: Resume at same dose 2nd appearance: Consider discontinuing pertuzumab ≥3rd appearance: Discontinue pertuzumab
	4	Hold palbociclib and pertuzumab until clinically stable and recover to ≤ Grade 1 or has returned to baseline, then 1st appearance: Resume pertuzumab at the same dose level. Resume palbociclib ≥ 2 weeks after resuming pertuzumab if clinically stable and ALT ≤ Grade 1. 2nd appearance: Discontinue palbociclib and pertuzumab
Concurrent > 3X ULN ALT (SGPT) and >2X ULN total bilirubin		Discontinue palbociclib and pertuzumab
Other AEs requiring dose modification per investigator (Note: Investigator must determine attribution of AE and only follow dose modifications for the causal agent.)	2	Lasting Less than 4 weeks: Maintain Dose Lasting 4 weeks (excluding alopecia) or more despite maximal supporting care unacceptable to patient and/or investigator, and thought to be related to palbociclib: resume at next lower dose
	3, 4	If the AE is related to palbociclib, withhold until symptoms resolve to: • ≤ Grade 1 or to baseline • ≤ Grade 2 (if not considered a safety risk for the patient) Resume at the next lower dose level.

Table 5: *AE-triggered Dose Modifications and Treatment Management for Trastuzumab and/or Pertuzumab*

Event	Grade	Action to Be Taken
Infusion-related reactions	Infusion-related symptoms Grades 1–2.	Decrease infusion rate by 50% or interrupt infusion for patients who experience any other infusion-related symptoms (e.g., chills, fever). When symptoms have completely resolved, infusion may be restarted at ≤ 50% of prior rate and increased in 50% increments every 30 minutes as tolerated. Infusions may be restarted at the full rate at the next cycle, with appropriate monitoring. In the event of a true hypersensitivity reaction (in which the severity of reaction increases with subsequent infusions) to trastuzumab or pertuzumab treatment, the respective agent must be permanently discontinued. Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids may be used as appropriate at the investigator's discretion. Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent infusions at the investigator's discretion. Patients should be monitored until complete resolution of symptoms.
	Grade ≥ 3 allergic/hypersensitivity reaction	Stop infusion. Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids may be used as appropriate at the investigator's discretion. Patients should be monitored until complete resolution of symptoms. Retreatment at subsequent cycle per investigator discretion.
Pneumonitis/ Interstitial Lung Disease	Grade 1 or 2	Discontinue pertuzumab regardless of attribution. Interrupt palbociclib as per instruction in Section 9.1.2
	Grade 3 or 4	Discontinue pertuzumab regardless of attribution. Discontinue palbociclib as per instruction in Section 9.1.2
Ejection fraction decreased	Grade 3 or 4	Discontinue trastuzumab and pertuzumab
Heart Failure	Grade 3 or 4	Discontinue trastuzumab and pertuzumab
Heart Failure Accompanied by LVEF <45%	Grade 2-4	Discontinue trastuzumab and pertuzumab
Asymptomatic decrease in LVEF	See Figure 2 on following page for dose modifications	

Figure 2: HER2-Directed Therapy Management Based on LVEF Assessments



LVEF = left ventricular ejection fraction; EF = ejection fraction % points
Note: Baseline refers to the screening LVEF.

Discontinuation of anti-HER2 therapy is recommended if LVEF recovery does not occur after three intermittent holds of study treatment but subsequent treatment is at investigator discretion on a case by case basis.

10. Study Phases

The study consists of 3 main phases which apply to both of Arms A and B:

- Screening Phase:
  - Preliminary Screening begins with the signing of the Preliminary Screening Consent
  - Randomization Screening Phase begins with the signing of the Main Study Consent
- Treatment Phase begins on the date of the C1D1 visit which is the start of study treatment and continues until patients stop treatment, enter one of the follow-up phases or complete the study.

- Follow-up Phase (Clinical Follow-up and Survival Follow-up) begins at the end of study treatment – meaning the end of **all** study treatments – palbociclib (if Arm A), endocrine therapy and anti-HER2 therapy, through end of study.

10.1 Screening

10.1.1 Preliminary Screening (pre-screening)

During the Pre-Screening Phase participants will be asked if they are willing to provide an archival tissue sample (mandatory), if they would like to participate in the MBC Initiative (optional), and if they would be willing to provide tissue from a biopsy of their metastatic disease site (optional). The Pre-Screening Consent will explain that participation in the MBC Initiative includes a provision that limited baseline clinico-pathologic characteristics and biomarker results (e.g. Genomic panel results) will be hosted in the MBC independent clinical data repository. The Pre-Screening ICF outlines the major goals of the MBC initiative and explains that this feature is optional.

- After signing the Pre-Screening Consent document, a formalin-fixed paraffin-embedded (FFPE) archival (primary breast or metastatic site) tumor tissue block or representative slides from such a block must be shipped to the AFT biorepository.
- An optional biopsy of metastatic disease (for patients with disease amenable to biopsy) should be performed preferably prior to the initiation of induction treatment. Tissue from a recently performed biopsy of metastatic disease is also acceptable.

Patients whose tumor samples are considered to be of low quality will be asked to resubmit additional tissue. Further details will be provided in the PATINA (AFT-38) Correlative Science Manual (CSM) which will be provided to all sites at study start-up.

Baseline clinico-pathologic features that will be collected during the screening phases of the study include (but are not limited to) the following:

1. Demographic data (gender, ethnicity, race, country of origin)
2. ECOG performance status
3. Menopausal status
4. Height, weight
5. Date of primary tumor diagnosis
6. Primary tumor characteristics at diagnosis
7. Prior treatments (surgery, radiation, chemotherapy, hormonal therapy)
8. Date of first known metastatic disease

The same information will be hosted in the MBC data repository for participants who consent to participate in the MBC Initiative.

Patients can sign the Pre-Screening Consent at any time during their induction therapy. Since 6-8 cycles of induction therapy are permitted (4 cycles if evidence of toxicity), the

time from signing the Pre-Screening Consent to the C1D1 visit could be up to 168 days. For patients who are early in their induction therapy, sites should wait before obtaining the Main Study Consent and beginning the eligibility assessments.

10.1.2 Randomization Screening

The Randomization Screening Phase begins after a patient provides written informed consent (Main Study Consent) to participate in the PATINA/AFT-38 research study. During this phase, all remaining Inclusion and Exclusion criteria will be assessed. Concomitant medications, medical history, physical examination/vital signs, ECOG performance status assessment, AEs, serious adverse events, laboratory measurements, pregnancy testing (if applicable), will be collected during this phase (see Study Assessment Table, Section 12).

All screening evaluations must be completed and reviewed to confirm that patients meet all inclusion criteria and do not meet any of the exclusion criteria before randomization.

The patient has a maximum of 28 days from the date the Main Study Consent is signed to determine eligibility and randomize the patient. Results of screening tests performed as standard of care prior to obtaining informed consent and within 42 days prior to randomization may be used rather than repeating required tests. (This does not apply to the baseline tumor assessments which must be done within 28 days of randomization). The actual date of randomization is the date the site randomizes the patient in the IRT system, which can occur up to 14 days prior to the C1D1 visit. In addition, screening assessments that are collected within 7 days of the C1D1 visit may serve as the C1D1 assessments and do not have to be repeated.

Since several of the study visits are intended to align with the patient's anti-HER2 infusion visits (for example the Arm A C1D22 visit for safety labs and the PK assessments), it is important to schedule the C1D1 visit on the date of a patient's anti-HER2 infusion.

In the Main Study Consent, patients will be asked to consent to an Optional Research biopsy or to provide tissue from a recently biopsied site of metastatic disease at disease progression. This is for future research associated with the MBC Initiative. Patients will be instructed that they can participate in the main study regardless of their decision to undergo this biopsy.

10.1.3 Screening Failures

Signed and dated ICFs for screened patients and for patients who are not subsequently enrolled or randomized in the study will be maintained at the study site. All screening evaluations must be completed and reviewed to confirm that patients meet all criteria before randomization.

Patients who complete the informed consent process but do not meet one or more eligibility criteria and therefore are not randomized will be considered screen failures.

Baseline genomic and clinico-pathologic data collected from patients who consented to the MBC Initiative will be stored in the MBC Data Repository regardless of whether these patients meet final eligibility to participate in this clinical study.

For all screen failures, clinical sites must enter minimal baseline information into the study EDC system using the appropriate CRFs.

Screen failures are allowed to be re-screened a single time only. All patients who are re-screened must be re-consented.

10.2 Treatment Phase

During this phase, patients randomized into Arm A will receive IP treatment (palbociclib) and Non-IP treatment and patients randomized into Arm B will receive Non-IP treatment only (anti-HER2 therapy plus endocrine therapy).

The Treatment Phase for patients on both Arms starts on Day 1 of Cycle 1 (C1D1), which should be on or shortly after the date the patient is randomized in the IRT system (within no more than 14 days). Arm A patients should begin IP treatment and both Arm A and Arm B should undergo an anti-HER2 infusion on this day.

Patients will continue with the Treatment Phase or begin the subsequent phases under the following conditions:

1) If any part of protocol treatment (IP or any part of Non-IP) is still being received, the patient will continue on the Treatment Phase. For example, if an Arm A patient discontinues palbociclib but remains on either or both of the other protocol-defined treatments (anti-HER2 and endocrine therapies), they would continue in the active Treatment Phase. If an Arm B patient stops anti-HER2 therapy but remains on endocrine therapy they would continue in the active Treatment Phase. This includes all visits and assessments required by the Schedule of Assessments table (see section 12) for this phase. Patients may remain on study treatment until they enter into one of the follow-up phases or reach End of Study.

2) Patients who discontinue ***all*** Study Treatment (Arm A: palbociclib, anti-HER2 therapy and endocrine therapy; Arm B: anti-HER2 therapy and endocrine therapy) due to a reason other than disease progression will move to the **Clinical Follow-up Phase**.

3) Patients who discontinue Study Treatment due to disease progression will move to the **Survival Follow-up Phase**.

4) Randomized patients on either Arm who are deemed ineligible prior to first dose or refuse to start their initial treatment will move to the Survival Follow-up.

   Patients who are deemed ineligible after starting protocol therapy will be discontinued from study treatment and will enter the Survival Phase of the study. In the event the ineligibility of a patient is not identified prior to starting treatment, continuation on

treatment will be reviewed on a case-by-case basis to evaluate any safety risks to the patient.

5) Withdrawal of consent for all study participation will end patient activity in the study and all follow up.

10.3 Treatment Discontinuation

The term "interruption" refers to a patient stopping the protocol therapy during the course of the study, but then re-starting it at a later time in the study. The reason for dosing interruption will be collected on the appropriate CRF.

The term "discontinuation" refers to a patient's withdrawal from the Treatment Phase, i.e., discontinues all IP and Non-IP therapy. The reason for discontinuation from treatment will be collected on the appropriate CRF.

If a patient opts to discontinue from the Treatment Phase as a result of an unacceptable adverse drug reaction, "withdrawal of consent" should not be the reason for discontinuation. Instead, the reason for discontinuation from the active Treatment Phase must be recorded in the “Off Treatment” eCRF as “Adverse Event/Side Effects/Complications.” The event should also be reported on the AE CRF with “Action Taken” recorded as discontinuation of treatment.

At the end of the study, for any patients who are still deriving clinical benefit from study treatment, the Sponsor will work with the investigator to explore options for alternative source of treatment, in accordance with local regulations and requirements.

10.4 Follow-Up Phase

10.4.1 End of Treatment Follow-up

Patients who discontinue treatment due to disease progression or who were deemed ineligible and removed from treatment will enter the Survival Follow-up Phase as discussed below. For these patients, the End of Treatment assessments can be those conducted at the study visit during which disease progression was determined, as long as all assessments were conducted at that visit (PROs, ECHO/MUGA, tumor scans, limited physical exam, etc.). If disease progression is determined in between study visits and the previous visit was more than 12 weeks prior, then an End of Treatment visit should be performed within 28 days of treatment discontinuation and all data collected.

Patients who discontinue all treatment for reasons other than disease progression should go into Clinical Follow-up and continue study visits every 12 weeks per the Schedule of Assessments.

The final sample for ctDNA should be collected at treatment discontinuation (+28 days).

10.4.2 Clinical Follow-up

For patients who discontinue all protocol Study Treatment for reasons other than disease progression, the patient will enter the Clinical Follow-up Phase. Patients will be seen in clinic every 12 weeks for imaging and assessment of adverse events per the Schedule of

Assessments/Clinical Follow-up Phase (see section 12) until disease progression. Once the patient progresses or initiates subsequent anti-cancer therapy (in the absence of progression), they will move to Survival Follow-up.

10.4.3 Survival Follow-up

For patients who progress during the Treatment Phase (or who were deemed ineligible and removed from treatment), the Clinical Follow-up Phase, or who are randomized but do not initiate protocol treatment, the patient will enter the Survival Follow-up Phase. When disease progression is confirmed the optional research biopsy or request for tissue from a recently biopsied metastatic site should be offered to patients who signed the Optional Research Biopsy question in the Main Study Informed Consent Form.

Survival data, ongoing treatments and subsequent disease progression data will be collected during this phase of the study. Telephone contact is acceptable as well as medical record review.

Follow-up will be discontinued early due to:

- Patient Death
- Patient Withdrawal of consent for all follow-up
- Patient deemed lost to follow-up

10.4.4 Study Discontinuation

Lost to Follow-up

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. If after two years of unsuccessful attempts to contact the patient, one of which is by registered letter, the patient cannot be reached, the patient should be considered "lost to follow-up." Steps taken to contact the patient (e.g., dates of telephone calls, registered letters, etc.) must be clearly documented in the patient's source documents.

Withdrawal of Consent

In any circumstance, every effort should be made to document patient status. If the patient can be reached and requests withdrawal from the study, the investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

Data to be collected for the end of study treatment/withdrawal are described in the Schedule of Assessments (Section 12). If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

The reason for treatment discontinuation must be entered into the appropriate eCRF. Patients who discontinue treatment will remain on study in the Follow-up Phase (either Clinical or Survival depending upon their disease status).

10.5 End of Study

The end of study will occur approximately 5 years after the last patient is randomized.

11. Study Assessments and Procedures

11.1 Medical History and Demographic Data

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 may be considered postmenopausal if one of the following criteria applies:

- Prior bilateral oophorectomy OR
- Age ≥ 60 years OR
- Age < 60 years with intact uterus and amenorrhea for ≥ 12 consecutive months* prior to chemotherapy and/or endocrine therapy exposure OR
- Age < 60 years hysterectomized and FSH and plasma estradiol levels in the post-menopausal range according to local policies prior to chemotherapy and/or endocrine therapy exposure

*This criterion might not apply to patients younger than 60 years in case they were concurrently using hormone replacement therapy, oral or any other hormonal contraceptives (such as hormonal contraceptive coil etc.).

If none of the above mentioned criteria fully apply, the patient may be judged premenopausal according to local policies. However, in case of any doubts, investigator's judgment on menopausal status is desirable and has to be documented in patient's notes and the eCRF.

Previous type of neoadjuvant and/or adjuvant therapy (i.e. chemotherapy, radiation etc.) including start date and end date must be recorded on the electronic Case Report Form (eCRF) by the investigator or delegate at site.

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

11.2 Concomitant Medications

Any concomitant medications and treatments that a patient is or has been taking from 30 days prior to randomization up to the end of the Treatment Phase should be recorded on the appropriate CRF at each study visit. Endocrine therapy is not considered concomitant medication and needs to be recorded separately on the appropriate eCRF.

11.3 ECOG Performance Status

The ECOG Performance Status should be assessed prior to randomization and on Day 1 of Cycles 1, 2, 3, and 4 and every 12 weeks thereafter, with the last assessment at the End of Treatment visit.

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

11.4 Complete Physical Exam

A complete physical exam should be conducted prior to randomization and should include an evaluation of head, eye, nose and throat, and cardiovascular, respiratory, gastrointestinal, and neurological systems as well as a measurement of weight and height.

11.5 Limited Physical Exam

A limited physical exam should be conducted monthly on Day 1 of Cycles 1, 2, 3, and 4 and every 12 weeks thereafter. This examination is a limited, symptom-directed examination which should include any of the assessments conducted in the complete physical as clinically indicated.

11.6 Vital Signs

Vital signs should be collected monthly on Day 1 of Cycles 1, 2, 3, and 4 and every 12 weeks thereafter. Measurements include respiratory rate, pulse, and systolic and diastolic pressure.

11.7 CBC and Platelets

CBC includes hemoglobin, white blood cell count (WBC) with differential, ANC, and platelet count. CBC will be collected monthly on Day 1 of Cycles 1, 2, 3, and 4 and every 12 weeks thereafter, with additional assessments as clinically indicated. In addition, subjects randomized to Arm A will have these labs performed on Day 22 of Cycle 1. These labs will be assessed at each site's local lab with results entered into the appropriate eCRF. It is strongly recommended that these assessments be performed at the research center lab. If this is not feasible, laboratory tests for individual patients should be performed at the same laboratory.

11.8 Blood Chemistry

Blood chemistry will be collected monthly on Day 1 of Cycles 1, 2, 3, and 4 and every 12 weeks thereafter, with additional assessments as clinically indicated. Blood chemistry includes AST (SGOT)/ALT (SGPT), alkaline phosphatase, sodium, potassium, total calcium, total bilirubin, serum creatinine, total protein and albumin. Additional hematology/chemistry panels may be performed as clinically indicated. All blood chemistries will be assessed at each site's local lab with results entered into the appropriate eCRF. It is strongly recommended that these

assessments be performed at the research center lab. If this is not feasible, laboratory tests for individual patients should be performed at the same laboratory.

11.9 Pregnancy Test

A serum pregnancy test should be performed within 7 days of randomization for women of childbearing potential, including premenopausal women who have had a tubal ligation, and premenopausal women who have chemotherapy-induced amenorrhea (includes women with amenorrhea induced by chemotherapy during the Induction Phase prior to study randomization).

Afterward, perform every 12 weeks (± 2 days) on urine or serum until disease progression. A positive urine pregnancy test must be confirmed with a serum pregnancy test.

Note: Serum or urine pregnancy test must be negative in women judged premenopausal within 7 days of randomization, or in women with amenorrhea of less than 12 consecutive months at time of randomization. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation.

11.10 ECG - Electrocardiogram (12-Lead ECG)

At screening, a single standard 12-lead resting ECG will be performed according to each site's standard of care process.
ECGs will be analyzed locally at each site. Parameters including heart rate, rhythm, and RR, PR, QRS and QTc intervals should be assessed to determine eligibility into the study (see Exclusion Criteria 5 and 8).

11.11 MUGA or Echocardiogram (ECHO)

ECHO/MUGA should be performed prior to randomization and repeated on Day 1 of Cycle 4 and every 12 weeks thereafter (±7 days), with additional examinations as clinically indicated. Left ventricular ejection fraction (LVEF) by ECHO is preferred. The same method should be used throughout the study for each patient and preferably performed and assessed by the same assessor. ECHO/MUGA should also be performed at Treatment Discontinuation if not done within the previous 12 weeks.

11.12 Tumor Assessments

The importance of timely and complete disease assessments in the study cannot be understated. Disease assessments must be performed as scheduled according to the study calendar to prevent the introduction of bias into the assessment of efficacy.
Screening/baseline tumor assessment will be carried out within 28 days of randomization (unless otherwise as specified below).

11.12.1 Imaging Assessment Collection Plan

Disease assessment for patients at baseline will include:

- CT or MRI scan of the chest, abdomen, and pelvis.
- Bone scans or PET scan in order to detect bony sites of disease. Any suspicious abnormalities (i.e., hotspots) identified on the bone scans at baseline must be confirmed by X-ray, CT scan with bone windows or MRI.
- Baseline brain CT or MRI are only required in case signs and symptoms suggest the presence of metastatic brain disease.
- CT or MRI scan of any other sites of disease as clinically indicated.

Post-baseline tumor assessments will be performed every 12 weeks (± 7 days) from C1D1 (to align with visit schedule) until disease progression with additional scans when clinically indicated. If a tumor assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule. Radiologic tumor assessment must include CT and/or MRI of the chest, abdomen and pelvis. Additional imaging should be performed if clinically indicated. The same imaging modality used at screening must be used throughout the study.

All scans throughout the study from baseline until disease progression will be uploaded to the Alliance Foundation Trials (AFT) Imaging Core Lab (ICL) at the Wright Center of Innovation in Biomedical Imaging (WCIBMI) at the Ohio State University. Complete imaging data sets in digital DICOM format will be collected and submitted electronically to the AFT ICL. Detailed instructions are provided in the AFT ICL Manual which will be provided to all sites during study start-up.

Patients who are discontinued from study treatment for reasons other than disease progression (Clinical Follow-up) will be asked to continue to have tumor assessments every 12 weeks (± 7 days) until disease progression or initiation of other anti-cancer therapies.

An isotope bone scan (e.g., technetium) or PET scan should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions or for confirmation of complete response for all patients. For patients with bone-only disease not visible on the CT or MRI scans being performed as part of the tumor assessments, bone scans or PET scan should be repeated every 12 weeks (± 7 days) from the C1D1 visit until disease progression. These scans will be submitted to the AFT ICL as well.

11.13 Patient Reported Outcome (PRO) Assessments

Patient reported outcomes of breast cancer specific health-related quality of life and health status will be assessed using validated questionnaires: The Functional Assessment of Cancer Therapy-Breast (FACT-B) and EuroQol-5D (EQ-5D) respectively [37, 38]. The FACT-B and EQ-5D will be given to the patient in the appropriate language for the site.

Patients will complete each instrument pre-dose on Day 1 of Cycles 1 and 4 and then Day 1 every 12 weeks over the course of treatment until disease progression, or study treatment discontinuation and at end of treatment visit.

Patients must complete these instruments in clinic (cannot be taken home) prior to having any tests and to any discussion of their progress with healthcare personnel at the site. Interviewer administration in clinic may be used under special circumstances (e.g. patient forgot their glasses or feels too ill). Completed questionnaires are always considered source documents and must be filed accordingly.

Functional Assessment of Cancer Therapy (FACT-B)

The FACT-B consists of the Functional Assessment of Cancer Therapy-General (FACT-G) (27-items) and a breast-specific module: a 10-item instrument designed to assess patient concerns relating to BC. The FACT-G is a 27-item compilation of general questions divided into 4 domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. Patients are asked to respond to a Likert scale where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much. (Brady et al 1997)

Euroqol-5D (EQ-5D)

The EuroQol EQ-5D is designed to assess health status in terms of a single index value or utility score. It contains 5 descriptors of current health state (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having 5 levels of function (1=no problem, 2=slight problem, 3=moderate problem, 4=severe problem, and 5=unable/extreme). The scores on the 5 descriptors are summarized to create a single summary score. The EQ-5D also includes a visual analog scale (VAS), in which the patients self-rate their overall health status on a scale from 0 (worst imaginable) to 100 (best imaginable) [38].

11.14 IP Dispensing

For palbociclib administration, please refer to Section 8.1.

11.15 Trastuzumab and Pertuzumab

The anti-HER2 therapies, trastuzumab and pertuzumab, should be administered every three weeks starting on Day 1 of Cycle 1. For additional information, please refer to Section 12, Study Assessment Table and Sections 8.3 and 8.4.

11.16 Survival Follow-up

Following disease progression and the End of Treatment visit, survival data and follow-up information will be collected in all patients every 6 months (± 14 days) until the end of the study. In addition to survival information, the study will collect treatment information beyond disease progression and patterns of disease progression (i.e., sites of metastatic disease progression).

11.17 Biomarker/Correlative Studies

Please see the AFT-38 (PATINA) Correlative Science Manual (CSM) for further specifics regarding biospecimen collection, processing, and shipping. The most current version of the AFT-38 CSM can be found on the AFT BioMS web site which is accessible via the AFT portal: (https://alliancefoundationtrials.org)

11.17.1 Biomarker/Correlative Studies: Circulating Tumor DNA (ctDNA) and Germline DNA

For assessment of germline DNA, one 10 mL lavender top (EDTA) tube of blood will be collected on Day 1 of Cycle 1 and Day 1 of Cycle 4.

For assessment of circulating tumor (ctDNA), two 10mL Streck tubes of blood will be collected on Day 1 of Cycle 1, Day 1 of Cycle 4, and at treatment discontinuation (+28 days). These tubes will be collected at each site's local lab and then shipped to the study central lab (outside US sites) or AFT Biorepository (US sites) for processing, storage, and analyses.

Collection of biospecimens is mandatory, unless specifically prohibited by local regulations.

Specific instructions for the sample collection, preparation, storage, labeling, and shipment of biospecimens is provided in the Central Lab/Biorepository Manual of Procedures. Sample shipment to the respective central sample repository may only be performed following patient consent and allocation of the study specific patient identification number to each sample.

11.17.2 Primary Breast Tumor Tissue

Submission of a representative archival (primary breast or metastatic site) formalin fixed and paraffin embedded (FFPE) tumor tissue sample is required from all patients prior to randomization. The archival tumor tissue specimen can be from a primary lesion, and may represent tissue obtained at the time of, or subsequent to, the initial diagnosis It would be preferable if the tumor tissue was collected within 6 months of enrollment into the trial to provide the most up-to-date information regarding the tumor and its microenvironment. Archived (primary breast or metastatic site) tumor tissue should be provided as ONE representative FFPE tumor tissue block containing sufficient tumor tissue to allow for sectioning of at least fifteen (15) slides each containing a 5-micron tissue section. All blocks will be returned at the end of the study or before, upon written request, if needed for specific patient clinical management. If a tissue block cannot be provided, sites should submit 15 freshly cut unstained slides, each containing a 5-micron tissue section cut serially from the same block.

If existing FFPE tissue from a diagnostic or clinical procedure is not available, a new, 'research only' primary tumor biopsy sample must be obtained in accordance with local institutional practice for tumor biopsies.

11.17.3 Biopsies of Metastatic Disease

Screening Phase: In addition to archival tumor tissue, it is strongly encouraged to obtain a representative biopsy of a locally recurrent or metastatic tumor lesion. The biopsy may be performed any time after a patient is determined to be eligible for the Study and has signed the Consent to the Screening phase of the study. Biopsies of locally recurrent or metastatic lesions should be performed according to standard institutional procedures. Providing tissue from a recently collected biopsy of the metastatic disease site is also permitted.

Please see the PATINA (AFT-38) Correlative Science Manual (CSM) for further specifics regarding biospecimen collection, processing, and shipping. The most current version of the PATINA CSM can be found on the AFT BioMS web site which is accessible via the AFT portal: (https://alliancefoundationtrials.org)

The recommendations described below for the amount of tissue to be obtained at the biopsy are not meant to replace clinical judgment at the time the procedure is performed. Less than the goal quantity of tissue is accepted for each type of biopsy and will be left to the clinical judgment of the physician performing the procedure. Note that new biopsies of recurrent or metastatic disease submitted will be for 'research purposes only.' They will not be used to make or confirm a diagnosis of metastatic breast cancer. Therefore, if required by clinical judgment, such biopsies should be submitted for local pathology diagnosis before or in addition to submission for correlative science studies.

Core biopsies are preferred; punch biopsies may be done when necessary, but fine needle aspirates are not acceptable.

- Breast: A goal of 3-6 core biopsy specimens will be obtained using standard institutional guidelines for a diagnostic core biopsy of a breast mass
- Skin/Chest wall: A goal of three 5-mm punch biopsies will be obtained
- Lymph node/Soft tissue: A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle if possible.
- Liver: A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle if possible.
- Lung: Because of the risk of pneumothorax associated with core needle biopsies of lung nodules, no core biopsies of lung nodules are recommended on this protocol; unless they are clinically indicated.
- Bone: Because the yield of malignant tissue from bone biopsies tends to be relatively low, if a patient has another accessible site of disease (e.g., skin, lymph node, liver), that site should be biopsied preferentially. If bone is the only biopsy-accessible site, then a goal of 1-3 core biopsy specimens will be obtained using an 11 to 13-gauge needle if possible.
- If ascites or pleural fluid is to be used as the investigational biopsy specimen, consideration should be given to confirming the malignant nature of the ascites or pleural fluid prior to study entry.

Disease Progression: In addition, a recommended but optional de novo tumor biopsy or tissue from a recently biopsied metastatic site may also be obtained at disease progression. This biopsy may be performed on a locally recurrent or a metastatic lesion.

Please refer to AFT-38 (PATINA) Correlative Science Manual (CSM) for a detailed description of collection, processing, and shipping procedures. The most current version of the PATINA (AFT-38) CSM can be found on the AFT.BioMS web site which is accessible via the AFT portal: (https://alliancefoundationtrials.org).

11.17.4 Pharmacokinetic (PK) Assessments

PK samples will be collected for Arm A participants enrolled in the United States only.

Palbociclib Pharmacokinetic (PK) Assessments

Plasma PK samples for palbociclib determination will be collected on Cycle 1 Day 22, as described in the Study Assessment Table. Patients must have received at least 7 consecutive days

of palbociclib before PK assessments on Cycle 1 Day 22, and the prior infusion of trastuzumab (3 weeks earlier) administered as scheduled.

Additional instructions for PK sampling include the following:

- The palbociclib dose that is taken on C1D21 should be at least 20 hours from the time the PK sample is drawn on C1D22. Patients should record the time of their C1D21 palbociclib dose in the patient diary.

In the event PK sample cannot be collected (or is not collected) on C1D22, every effort should be made to collect makeup samples on any day from Day 8 to Day 22 of later cycles, using the same criteria. The exact time of the sample collection and the most recent dosing time before and after PK sample collection if applicable will be recorded on the eCRF. The date of missing dose should also be recorded in the eCRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing (predose samples are approximately 24 hours post the last dose). However, samples obtained within 10% of the nominal time (i.e., 2.4 hours) will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (e.g., CRF/DCT).

During all study periods, blood samples (3 mL) to provide approximately 1 mL of plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) at protocol-specified times.

Please refer to the AFT-38 CSM for details on collection, processing and shipping procedures. The most current version of the PATINA (AFT-38) CSM can be found on the AFT BioMS web site which is accessible via the AFT portal (https://alliancefoundationtrials.org).

Trastuzumab Pharmacokinetic (PK) Assessments
Serum PK samples for trastuzumab determination will be collected prior to IV infusion (predose) on C4D1 as described in the Study Assessment Table. Patients must have received at least 3 cycles of trastuzumab before PK assessments on C4D1 and the last trastuzumab dose prior to PK sampling administered as scheduled.

In the event PK sample cannot be collected (or is not collected) on C4D1, every effort should be made to collect makeup samples on later trastuzumab administration days using the same criteria. The date of missing dose should also be recorded in the CRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing.

During all study periods, blood samples (3 mL) to provide approximately 1 mL of serum for pharmacokinetic analysis will be collected into appropriately labeled tubes containing no additives at protocol-specified times.

Please refer to the AFT-38 CSM for details on collection, processing and shipping procedures. The most current version of the PATINA (AFT-38) CSM can be found on the AFT.BioMS web site which is accessible via the AFT portal: (https://alliancefoundationtrials.org).

Pertuzumab Pharmacokinetic Assessments

Serum PK samples for pertuzumab determination will be collected prior to IV infusion (predose) on C4D1 as described in the Study Assessment Table. Patients must have received at least 3 cycles of pertuzumab before PK assessments on C4D1, and the last dose of pertuzumab prior to the PK sample collection administered as scheduled.

In the event PK samples cannot be collected (or is not collected) on C4D1, every effort should be made to collect makeup samples on later pertuzumab administration days using the same criteria. The date of missing dose should also be recorded in the CRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing.

During all study periods, blood samples (3 mL) to provide approximately 1 mL of serum for pharmacokinetic analysis will be collected into appropriately labeled tubes containing no additives at protocol-specified times. Samples will be kept in an ice bath prior to processing.

Please refer to the AFT-38 CSM for details on collection, processing and shipping procedures. The most current version of the PATINA (AFT-38) CSM can be found on the AFT.BioMS web site which is accessible via the AFT portal: (https://alliancefoundationtrials.org).

11.18 Treatment Adherence

Drug Diaries will be maintained for all patients to capture adherence to palbociclib. Diaries will be completed by the patient and subsequently reviewed for accuracy with the patient at each visit. Patients will also be asked to bring in their pill containers at each visit, whether empty or still containing study medication. Pill counts of palbociclib will be performed and recorded at each study visit by research staff. If the patient's pill count of palbociclib is discrepant with the Drug Diary, the pill count will be used to determine adherence status. Patients found to be non-adherent with their medications may receive additional interventions by the treatment team to improve adherence (i.e. phone calls may be employed as a first-line intervention and extra study visits may be scheduled if non-adherence is still noted at the follow-up time point).

Data from the Drug Diaries will be entered into the eCRF. For each 28-day cycle, data regarding the number of days palbociclib was taken (start and stop dates per cycle along with any dose holds) will be entered into the eCRF. Adherence to study treatment will be determined by number of days taken / number of days drug should have been taken over various time points during the study.

The frequency of assessments is provided in the Study Assessment Table (Section 12).

12. Study Assessment Table

			Treatment Phase (cycle = 28 days)																	
	Preliminary Screening **a**	Screening/ Randomization **a, b**	Cycle 1				Cycle 2				Cycles 3				Cycle 4 + **d**				Every 3 Cycles (12 wks) until disease progression	End of Treatment **bb**
Day			D 1	D 8	D 15	D 22 **c**	D 1	D8	D 15	D 22	D 1	D8	D 15	D 22	D1	D 8	D 15	D 22	D1	Within 28 days after determination of disease progression and/or last dose (These assessments do not need to be repeated if collected within 12 weeks of determination of disease progression or end of treatment)
(Window in days)	Any time during induction	-28 days	+14			± 2	± 2				± 2				± 2				± 2	
Informed Consent **e**	X	X																		
Inclusion/Exclusion Criteria	X	X																		
Medical History **f**		X																		
Concomitant Medications **g**		X	X				X				X				X					X
ECOG Performance Status **h**		X	X				X				X				X				X	
Complete physical exam **i**		X																		
Limited Physical Exam **j**			X				X				X				X				X	X
Vital signs **k**		X	X				X				X				X				X	X

			Treatment Phase (cycle = 28 days)																	
	Preliminary Screening **a**	Screening/ Randomization **a, b**	Cycle 1				Cycle 2				Cycles 3				Cycle 4 + **d**				Every 3 Cycles (12 wks) until disease progression	End of Treatment **bb**
Day			D 1	D 8	D 15	D 22 **c**	D 1	D8	D 15	D 22	D 1	D8	D 15	D 22	D1	D 8	D 15	D 22	D1	Within 28 days after determination of disease progression and/or last dose (These assessments do not need to be repeated if collected within 12 weeks of determination of disease progression or end of treatment)
(Window in days)	Any time during induction	-28 days	+14			± 2	± 2				± 2				± 2				± 2	
Adverse Events **l**	X	X	X				X				X				X					X
CBC and platelets **m**		X	X			X	X				X				X				X	
Blood chemistry **n**		X	X				X				X				X				X	
Pregnancy test **o**	X	X													X				X	
ECG **p**		X																		
MUGA or echocardiogram (ECHO) **q**		X	MUGA or ECHO (±7-day window)																	X
															X				X	
Tumor assessments: CT and/or MRI of chest, abdomen, pelvis **r**		X	Tumor Assessments (±7-day window)																	X
															X				X	
Tumor assessments: Bone or PET scan **s**		X													X				X	X
Archival FFPE tumor tissue **t**	X																			

			Treatment Phase (cycle = 28 days)																	
	Preliminary Screening **a**	Screening/ Randomization **a, b**	Cycle 1				Cycle 2				Cycles 3				Cycle 4 + **d**				Every 3 Cycles (12 wks) until disease progression	End of Treatment **bb**
Day			D 1	D 8	D 15	D 22 **c**	D 1	D8	D 15	D 22	D 1	D8	D 15	D 22	D1	D 8	D 15	D 22	D1	Within 28 days after determination of disease progression and/or last dose (These assessments do not need to be repeated if collected within 12 weeks of determination of disease progression or end of treatment)
(Window in days)	Any time during induction	-28 days	+1 4			± 2	± 2				± 2				± 2				± 2	
Tissue from metastatic tumor biopsy **u**	X																			X
One 10 mL lavender top (EDTA) tubes of blood **v**			X												X					
Two 10 mL Streck tubes of blood **w**			X												X					X
PK 3 mL of blood for each PK assessment (palbociclib, trastuzumab, pertuzumab) **x**						X									X					
PRO assessments **y**			X												X				X	X
IP (Palbociclib) Dispensing **z**			X				X				X				X				X	

			Treatment Phase (cycle = 28 days)																	
	Preliminary Screening **a**	Screening/ Randomization **a, b**	Cycle 1				Cycle 2				Cycles 3				Cycle 4 + **d**				Every 3 Cycles (12 wks) until disease progression	End of Treatment **bb**
Day			D 1	D 8	D 15	D 22 **c**	D 1	D8	D 15	D 22	D 1	D8	D 15	D 22	D1	D 8	D 15	D 22	D1	Within 28 days after determination of disease progression and/or last dose (These assessments do not need to be repeated if collected within 12 weeks of determination of disease progression or end of treatment)
(Window in days)	Any time during induction	-28 days	+1 4			± 2	± 2				± 2				± 2				± 2	
Trastuzumab and/or Pertuzumab **aa**			X			X			X			X			X			X		

a. Preliminary Screening (pre-screening) Phase: Patients may be screened before or during induction treatment with anti-HER2 based therapy for the treatment of metastatic breast cancer prior to study randomization. If a patient is just starting induction, the time from signing the Pre-Screening Consent to randomization could be up to 8 cycles or 168 days. If a patient has completed induction therapy, the time from their last infusion to C1D1 can be no longer than 12 weeks. Following the pre-screening consent, an archival (primary breast or metastatic site) formalin-fixed paraffin-embedded (FFPE) tumor tissue block or representative slides should be collected and submitted to the central biorepository. Optional research biopsy: representative tumor specimen from metastatic disease, is collected from consenting patients if clinically feasible.

b. Randomization Screening Phase: All screening evaluations must be completed and reviewed to confirm that patients meet all inclusion criteria and do not meet any of the exclusion criteria before randomization. All assessments should be complete and eligibility determined within 28 days of the patient signing the Main Consent Form. Results of screening tests performed as standard of care prior to obtaining informed consent and within 42 days prior to randomization may be used rather than repeating required tests. (This does not apply to the baseline tumor assessments which must be done within 28 days of randomization). If screening assessments occur within 7 days before Cycle 1 Day 1, then they may serve as the Cycle 1 Day 1 assessments and do not need to be repeated. Once all eligibility assessments are done and the patient is found to meet all eligibility criteria, the patient can be randomized in the IRT system. The C1D1 visit should occur within 14 days of IRT randomization and must align with the patient's anti-HER2 infusion schedule. The visit at which disease progression is recorded can be used as the study drug discontinuation visit as long as tests required at the End of Treatment are performed.

c. Patients in the palbociclib study arm only will have safety laboratory testing (i.e. CBC with differential and platelets) performed on Day 22 (± 2) of Cycle 1. Results can be checked by telephone contact only. Laboratory testing must be performed at the research center and telephone calls should occur after the laboratory testing is completed.

d. Trastuzumab and/or Pertuzumab infusion will follow the three-week interval which does not necessarily match to Day 8 in a given treatment cycle.
e. A Preliminary Screening Informed Consent Form will be provided to patients first to determine if they are willing to provide the mandatory archival tissue sample, an optional tissue sample from recent biopsy of metastatic disease, and optional participation in the Mastering Breast Cancer Initiative. It must be obtained before any of the above can occur. The Main Informed Consent Form must be obtained prior to any protocol required randomization screening assessments. which are not performed as part of local routine care.
f. 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. Demographic data includes age, sex, stratification factors, and self-reported race/ethnicity.
g. Any concomitant medications and treatments will be recorded from 28 days prior to randomization and until 42 days following confirmation of disease progression.
h. The ECOG Performance Status should be assessed prior to randomization and on Day 1 of Cycles 1-4 and every 12 weeks until disease progression.
i. Complete physical examination should include the evaluation of head, eye, nose, and throat, and cardiovascular, respiratory, gastrointestinal, and neurological systems and measurement of weight and height.
j. Limited physical examination should include a limited, symptom-directed examination or as clinically indicated. Limited physical examination will be performed on Day 1 of Cycles 1 to 4 and every 12 weeks thereafter, with additional examinations as clinically indicated.
k. Vital signs include measurements of respiratory rate, pulse, and systolic and diastolic pressure. Vital signs will be checked Day 1 of Cycles 1 to 4 and every 12 weeks thereafter, with additional examinations as clinically indicated.
l. For all enrolled patients, AEs must be reported from the date of first treatment (C1D1) until 42 days following confirmation of disease progression. SAEs need to be reported for 6 months following confirmation of disease progression. AEs that occur during the Screening Phase that are deemed to be related to any study specific procedure should be reported on the AE form in the clinical database. SAEs, including those fulfilling the criteria for expedited reporting must be reported within 24 hours of site awareness.
m. CBC includes hemoglobin, white blood cell count (WBC) with differential, absolute neutrophils, platelet count. CBC will be performed on Day 1 of Cycles 1 – 4 and every 12 weeks until disease progression, with additional examinations as clinically indicated. In addition, subjects in Arm A (palbociclib arm) will have these labs performed on Day 22 of Cycle 1 for safety testing.
n. Blood chemistry includes AST (SGOT)/ALT (SGPT), alkaline phosphatase, sodium, potassium, total calcium, total bilirubin, serum creatinine, total protein and albumin. Chemistry will be performed Day 1 of Cycle 1 to 4 and every 12 weeks thereafter, with additional examinations as clinically indicated. Additional chemistry panels may be performed as clinically indicated.
o. For women of childbearing potential, including premenopausal women who have had a tubal ligation, and premenopausal women who have chemotherapy-induced amenorrhea (i.e. amenorrhea induced by chemotherapy during the Induction Treatment Phase prior to study randomization). Screening assessment must be performed on serum or urine within 7 days prior to randomization. Afterward, perform every 12 weeks (±2days) on urine or serum until disease progression. A positive urine test must be confirmed with a serum test.
p. ECG (electrocardiogram). Single standard 12-lead digital ECGs will be performed at baseline as part of the screening assessments.
q. LVEF assessment by ECHO is preferred. The same method should be used throughout the study for each patient and preferably performed and assessed by the same assessor. ECHO/MUGA should be done at baseline and repeated on Day 1 of Cycle 4 (±7 days) and every 12 weeks thereafter, with additional examinations as clinically indicated. ECHO/MUGA should also be performed at Treatment Discontinuation if not done within the previous 12 weeks.

r. Perform tumor assessment at screening (≤ 28 days prior to randomization), every 12 weeks (± 7 days) from C1D1 (to align with visit schedule until disease progression with additional scans when clinically indicated. If a tumor assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule. Radiologic tumor assessment must include CT and/or MRI of the chest, abdomen and pelvis. Additional imaging should be performed if clinically indicated. The same imaging modality used at screening must be used throughout the study. Patients who are discontinued from study treatment for reasons other than disease progression will be asked to continue to have tumor assessments every 12 weeks (± 7 days) until disease progression or initiation of other anti-cancer therapies.
s. An isotope bone scan (e.g., technetium) or PET scan will be performed at screening and should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions or for confirmation of complete response for all patients. For patients with bone-only disease not visible on the CT or MRI scans being performed as part of the tumor assessments, bone scans or PET scan should be repeated every 12 weeks (± 7 days) from C1D1 (to align with visit schedule) until disease progression.
t. Archival (primary breast or metastatic site) tumor tissue blocks or a minimum of 15 freshly cut unstained slides from the most recent tumor tissue will be collected at screening for molecular characterization of the tumor tissue.
u. Tissue from metastatic disease (optional): Tissue from recurrent / metastatic tumor biopsy collected at any time prior to screening for the purpose of molecular characterization (i.e. multigene panel). Tissue from tumor biopsy collected at the time of disease progression is strongly recommended and will be collected for patients who consent to provide this optional tissue.
v. Blood will be collected and banked in order to extract germline DNA to be used as normal DNA reference for tumor tissue-based studies. This will be collected on Day 1 of Cycle 1 and Day 1 of Cycle 4.
w. Blood will be collected to assess circulating tumor DNA (ctDNA) on Day 1 of Cycle 1 and Day 1 of Cycle 4 and at end of treatment (+28 days).
x. PK assessments for participants enrolled in the US only (Arm A only): A sample of 3 mL of blood for palbociclib PK determination will be collected on Day 22 of Cycle 1. Patients must have received at least 7 consecutive days of palbociclib before palbociclib PK sample collection and the last trastuzumab dose prior to the PK sampling administered as scheduled. A sample of 3 mL of blood for trastuzumab PK determination will be collected on Day 1 of Cycle 4 prior to IV infusion. Patients must have received at least 3 cycles of trastuzumab before trastuzumab PK sample collection on C4D1, and the last dose of trastuzumab prior to the PK sample collection administered as scheduled. A sample of 3 mL of blood for pertuzumab PK determination will be collected on Day 1 of Cycle 4 prior to IV infusion. Patients must have received at least 3 cycles of pertuzumab before pertuzumab PK sample collection on C4D1, and the last dose of pertuzumab prior to the PK sample collection administered as scheduled.
y. Patient reported outcome (PRO) assessments (FACT-Breast and EQ-5D) will be completed by patients on Day 1 of Cycle 1 and Cycle 4 and then every 12 weeks until disease progression or end of study treatment. Final PROs at disease progression only need to be completed if not done within the previous 12 weeks.
z. Patients will receive amount of IP in order to ensure sufficient supply until the next scheduled onsite visit (3 weeks of IP dispensed on Day 1 of Cycles 1, 2, and 3; 12 weeks of IP on Day 1 of Cycle 4 and every 12 weeks thereafter until end of treatment or disease progression). The visit window for all visits and hence IP dispensing is ± 2 days from each visit. However, it is important for all Arm A patients to follow the 28-day cycle (21 days on IP, 7-day break) as outlined. If the visit is scheduled 2 days early (-2 days), the patient should be instructed to wait until the 7-day break is completed before beginning their next 21-day cycle of IP. Subsequent visits should be scheduled 28 days from the date the current cycle will have ended. If the visit is scheduled 2 days late and the drug holiday is thus 9 days, the next visit should be scheduled 28 days from the actual visit date. Any deviations from the protocol defined IP schedule need to be reported as protocol deviations. Drug Compliance for IP will be assessed by drug accountability (patients are requested to return any used and unused bottles of IP at their next scheduled onsite visit). Furthermore, patients are requested to complete IP Drug Diaries, which also have to be returned at each onsite visit. At each visit, prior to IP

dispensation, an AE and laboratory-based assessment has to be performed by the investigator for evaluation of potential dose reduction obligations according to the protocol. There will be no drug accountability for Non-IP. However, compliance will be assessed at each patient onsite visit via Non-IP Drug Diaries completed by the patients. Patients are requested to bring Drug Diaries back to the site at each visit. IP Drug Diaries and/or Non-IP Drug Diaries should be collected during the Treatment Phase of the study.

aa. Trastuzumab and/or Pertuzumab will be administered every three weeks until end of treatment or disease progression.

bb. An additional End of Treatment visit is required only if the last study visit occurred more than 12 weeks from the determination of disease progression. In many cases, the assessments performed at the study visit during which disease progression was determined can be used as the End of Treatment assessments. Patients who discontinue treatment for reasons other than disease progression will go into Clinical Follow-up and continue visits every 12 weeks. The only exception is the final ctDNA sample which needs to be collected within 28 days after end of treatment.

	Follow-up	
	Clinical Follow-up (For patients who discontinue treatment for reasons other than disease progression)	**Survival Follow-up**
Day	Every 12 weeks until disease progression or end of study	Every 6 months until the end of the study
(Window in days)	± 2 days[c, d]	± 14 days
Adverse Events [a]	X	X
Serious Adverse Events [b]	X	X
Tumor assessment [c]	X	
Bone-scan or PET scan [d]	X	
Tissue from metastatic tumor research biopsy [e]		X
Treatment beyond disease progression [f]		X
Survival follow-up assessment [g]		X

a. AEs must be reported throughout the Clinical Follow-up period and Survival Follow-up period until 42 days following confirmation of disease progression.
b. SAEs must be reported for 6 months after last treatment with palbociclib (Arm A patients) and for 7 months after last treatment with trastuzumab (Arm A and Arm B patients). SAEs deemed related to IP treatment must be reported throughout both Follow-up Phases as well.
c. If a tumor assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule. Radiologic tumor assessment must include CT and/or MRI of the chest, abdomen and pelvis. Additional imaging should be performed if clinically indicated. The same imaging modality used at screening must be used throughout the study. Patients who are discontinued from study treatment for reasons other than disease progression will be asked to continue to have tumor assessments every 12 weeks (±7 days) until disease progression or initiation of other anti-cancer therapies.
d. An isotope bone scan (e.g., technetium) or PET scan will be performed in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions or for confirmation of complete response for all patients. For patients with bone-only disease not visible on the CT or MRI scans being performed as part of the tumor assessments, bone scans or PET scan should be repeated every 12 weeks (±7 days) from C1D1 (to align with study visits until disease progression. All scans should be uploaded to the Alliance Central Imaging Core Lab (ICL) at the Wright Center of Innovation in Biomedical Imaging at the Ohio State University according to the instructions provided in the ICL Manual.
e. Tumor biopsy or tissue collection of recently biopsied site at the time of disease progression is strongly recommended and will be collected for patients who sign the Optional Research Informed Consent Form.
f. Collection of treatment information beyond disease progression with a focus on anti-cancer agents for all patients who discontinue from the treatment phase unless the patient requests to be withdrawn from study survival follow-up .
g. All patients who discontinue from the treatment phase will be followed for survival unless the patient requests to be withdrawn from study survival follow-up. For patients who discontinue study treatment due to objective disease progression, survival data (i.e., patient status along with start, stop and type of new anticancer therapy) will be collected every 6 months (±14 days), calculated from the last dose of study treatment until the end of the study. Telephone contact is acceptable.

13. Adverse Events

Palbociclib is currently approved in the US for metastatic breast cancer and is currently in clinical development. Therefore, the entire safety profile is not known at this time and human experience is currently limited. Currently available information is based on results from ongoing clinical studies. The following safety instructions and guidance for this study are designed to ensure patient safety and will include specific eligibility criteria, safety reporting obligations and monitoring assessments as detailed below.

13.1 Adverse Events – General Overview

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

a. Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure whether or not considered related to the use of the medicinal product or protocol-specified procedure.
b. Any worsening (i.e. any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of an investigational/medicinal product

For each AE recorded on an AE eCRF page, the investigator will make an assessment of seriousness, severity, and causality as described below).

13.1.1 Adverse Events – Palbociclib

The list of palbociclib associated AEs are summarized below. A detailed description of palbociclib associated AEs should be obtained from the palbociclib Investigator's Brochure. Additional reference to safety information can be found in Section 1.2.7 of this document.

Likely (greater than or equal to 50% chance that this will happen):

- Neutropenia. A condition in which the number of white bloods cells called neutrophils is abnormally low. This increases the risk of infection, which may be serious or life threatening. You will be monitored closely for this risk.

Frequent (between a 10 to 50% chance that this will happen):

- Fatigue. Participants experiencing fatigue while taking palbociclib should exercise caution when driving or operating machinery.
- Weakness
- Low number of red blood cells that can causes tiredness and shortness of breath. May require a blood transfusion. (Anemia)
- Diarrhea
- Nausea
- Low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion.
- Decreased appetite

- Constipation
- Mouth blisters/sores
- Infection of the sinus or lung
- Vomiting
- Loss of touch or sensation of pins and needles or numbness on the skin

Occasional (Between a 1 to 10% chance that this will happen):

- Rash
- Bloating
- Temporary hair loss
- Swelling in extremities (hands and feet)
- Headache
- Nosebleed
- Muscle spasm
- Inflammation of the mucous membranes
- Fever
- Dry mouth
- Fever with dangerously low white blood cell count
- Abnormal taste

Rare (Less than a 1 % chance that this will happen):

- Abnormal electrical conduction within the heart which may lead to arrhythmias or irregular heartbeat
- A blood clot that causes a sudden blockage in a lung blood vessel, usually due to a blood clot that traveled to the lung from the leg. A pulmonary embolism is a serious condition that can cause: permanent damage to part of your lung from lack of blood flow to lung tissue; low oxygen levels in your blood; damage to other organs in your body from not getting enough oxygen. If a clot is large, or if there are many clots, a pulmonary embolism can cause death.

13.1.2 Adverse Events – Endocrine Therapies

The most common AEs experienced with use of AIs include hot flashes, arthralgia, and gradual loss of bone density. The most common AEs experienced with use of fulvestrant are injection-site pain, nausea and bone pain.

A detailed description of AEs of the 3 AIs (letrozole, anastrozole, exemestane), LHRH Agonist and fulvestrant should be obtained from the particular package inserts (SmPCs) of the locally obtained commercial supplies.

13.1.3 Adverse Events – Anti-HER2 Therapies

The most common adverse reactions in patients receiving trastuzumab in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of trastuzumab treatment include congestive heart failure, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity.

The most common adverse reactions (> 30%) seen with pertuzumab in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy.

A detailed description of trastuzumab and pertuzumab should be obtained from the particular package inserts (SmPCs) of the locally obtained commercial supplies.

13.2 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 4.0) will be used for assessing AE severity. Table 8 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Table 7: *Adverse Event Severity Grading Scale*

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d Assessment of Severity of Adverse Events
5	Death related to adverse event [d]

NCI CTCAE National Cancer Institute Common Terminology Criteria for AEs. Note: Based on the most recent version of NCI CTCAE (v 4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a SAE (see Section 13.8.1 for reporting instructions), per the definition of SAE in Section 13.5.

[d] Grade 4 (only if immediately life threatening) and Grade 5 events must be reported as SAEs (see Section 13.8.1 for reporting instructions), per the definition of SAE in Section 13.5.

13.3 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the AE, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the IP or Non-IP, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 8: *Adverse Events - Causal Attribution Guidance*

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	Adverse events will be considered related, unless they fulfill the criteria as specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g. preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each of palbociclib, anti-HER2 and endocrine therapies. Investigator is responsible for reporting side effects of commercially available drugs to regulatory agency.

13.4 Adverse Event Reporting Period

AE data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the study as well as those who will enroll in future studies using similar agents. During Screening, baseline AEs will be considered part of a patient's underlying medical condition. If during Screening an AE occurs due to a required screening procedure (a blood draw, fresh tumor biopsy, or other protocol specified procedure or intervention), it should be reported on the AE form according to guidelines for standard AE reporting.

Any new AEs or worsening of a documented preexisting condition from screening/history will be recorded as an AE from the time of the first treatment (Cycle 1, Day 1) through 42 days following confirmation of disease progression and cessation of treatment.

All non-serious AEs are entered into the eCRF in RAVE EDC system **within 7 days** of the investigator's awareness of the event.

13.5 Serious Adverse Events (SAEs)

A SAE is any AE that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly/birth defect
- Is an Important Medical Event (ME) that may not result in death, be life threatening, or require hospitalization but, based upon the investigator's judgement, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above.

SAEs have to be reported on the AE form and on the study specific SAE reporting form in the RAVE EDC system within 24 hours of the site investigator's knowledge of this event.

In line with the AE reporting guidelines, during Screening only SAEs deemed related to a specific protocol screening procedure need to be reported. Once patients are randomized, the SAE reporting period starts at the time of the first treatment (Cycle 1, Day 1) through 6 months after last treatment with palbociclib (Arm A patients) and 7 months after last treatment with trastuzumab (Arm A and B patients). SAEs deemed to be related to IP treatment must be reported throughout both Follow-up Phases as well.

13.6 Adverse Events of Special Interest

Abnormal Liver Function Tests (LFTs) reported as Hy's Law
Investigators must report as a SAE the occurrence of either of the following:

- Treatment-emergent ALT or AST (>3x ULN) in combination with total bilirubin (>2 x ULN)
- Treatment-emergent ALT or AST (>3x ULN) in combination with clinical jaundice

The finding of an elevated ALT or AST (>3x ULN) in combination with either an elevated total bilirubin (>2x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury.

The most appropriate diagnosis or, if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the AE eCRF and reported to the AFT Safety Group immediately (no more than 24 hours after learning of the event) using the study specific SAE reporting way.

13.7 Suspected Unexpected Serious Adverse Reaction (SUSAR)

- An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a SAE/Reaction
- Qualifies for expedited IND safety reporting to the FDA, Competent Authorities and other regulatory bodies by meeting all three definitions of suspected adverse reaction, serious, and unexpected.
- Expected adverse reactions and related serious adverse reactions to palbociclib are listed in the Investigator Brochure (IB). The AFT Safety group will evaluate all SAEs reported in the RAVE database for expectedness against the most recent Investigator Brochure (IB) and will determine if a reported SAE meets the criteria of a SUSAR.

13.8 Expedited Reporting Procedures

13.8.1 Serious Adverse Event Reporting Timelines

All AEs need to be reported in the RAVE EDC system within 7 days of the investigator's knowledge of the event.

Certain events require immediate reporting. The following is a list of events that the investigator must report to the AFT Safety Group on the study specific SAE form **within 24 hours** after learning of the event, regardless of the relationship to study drug:

- Serious Adverse Events (SAEs), including:
  - Abnormal LFTs reported as Hy's Law
  - SUSARs
- Pregnancies
- Lactation Exposure

The investigator must also report new significant follow-up information for these events on the study specific SAE form to the AFT Safety Group immediately (no more than 24 hours after becoming aware of the information).

New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with requirements for reporting SAEs to the local IRBs/ECs and/or any other parties as locally required and if applicable.

13.8.2 Expedited Reporting to Regulatory Authorities

The Safety Management group at AFT will complete and submit expedited regulatory safety reports (SUSARs) on the required MedWatch or CIOMS templates to the relevant regulatory/competent authorities within the required reporting timelines. In general, AFT is required to report all non-fatal or non-life threatening SUSARs to the FDA and regulatory authorities outside the US within 15 calendar days of investigator awareness of the event and all fatal or life-threatening SUSARs within 7 calendar days of investigator awareness.

A comprehensive safety reporting process for this study is documented in the study Safety Management Plan.

13.8.3 Adverse Event Reporting Exceptions

Recurrence or progression of the underlying malignancy is reportable **only** if the patient dies due to disease recurrence or progression within the reporting period. Hospitalization solely due to the recurrence or progression of the underlying malignancy should not be reported as an SAE. Clinical symptoms of recurrence or progression may be reported as AEs if the symptom 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.

The following hospitalization scenarios are <u>not</u> considered to be AEs:

- Hospitalization for respite care
- Hospitalization for a preexisting condition provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study
    - The patient has not suffered an AE
- Hospitalization due solely to progression or recurrence of the underlying cancer
- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care
- Hospitalization for protocol mandated biopsies

14. Data Collection and Management/ Data and Specimen Submission

14.1 Data Collection and Submission

Data collection for this study will be done through the electronic Medidata RAVE clinical data management system. Access to the trial in RAVE is granted through the iMedidata application to all persons fulfilling Medidata RAVE training requirements and with the appropriate roles assigned in AFT's Clinical Trial Management System (CTMS). Specific instructions are provided in the study Data Entry Guidelines.

14.2 Specimen Collection and Submission

The following biospecimens will be collected during the study:

At Screening:

- Representative formalin-fixed paraffin-embedded (FFPE) archival (primary breast or metastatic site) tumor tissue block (preferred) or at least 15 unstained slides from such a block, along with a pathology report documenting HER2 positivity and hormone receptor positivity
- Representative tumor specimen obtained from recently biopsied metastatic disease, if clinically feasible (optional)

During Study:

- Germ Line DNA (whole blood for isolation of white cell (constitutional) DNA): Day 1, Cycle 1 and Day 1, Cycle 4
- Circulating tumor DNA (ctDNA): Day 1, Cycle 1; Day 1, Cycle 4, and end of treatment
- Tumor specimen at disease progression, if patient consents

For US sites, all biospecimen collection kits should be requested through the AFT.BioMS system which is accessible via the AFT portal (https://alliancefoundationtrials.org). Additional details for biospecimen collection, processing, and shipping can be found in the AFT-38 (PATINA) Correlative Science manual (CSM), which is also available on the AFT.BioMS web site via the AFT portal (https://alliancefoundationtrials.org).

15. Measurement of Effect

15.1 Imaging Assessment Collection Plan

Refer to section 11.11.1 about the collection of imaging assessments and submission to the Wright Center of Innovation in Biomedical Imaging at the Ohio State University (the Alliance central Imaging Core Lab).

Post-baseline tumor assessments will be performed every 12 weeks (± 7 days) after the C1D1 visit (to align with study visits until disease progression with additional scans when clinically indicated.

For patients having effusions or ascites, cases having cytological proof of malignancy should be recorded as non-target lesions on the tumor assessment CRFs. Effusions that

have not been evaluated using cytology or were found to be non-malignant should not be recorded on the non-target lesion CRF.

Objective tumor response will be assessed using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Interpretation will be Progressive Disease if:

- The malignant nature of one or more new lesions identified with bone scan is confirmed with X-ray, CT, or MRI scan.
- Flare observed in bone scan is followed by confirmation of progression with other imaging modalities.
- Clinical worsening of the disease is assessed by bone scan and disease progression (i.e. new lesion(s) is confirmed with other imaging modalities).
- Unequivocal progression of existing bone lesions is observed.

Interpretation will be SD if:

- The malignant nature of all the new lesions identified with bone scan is not confirmed with X-ray, CT, or MRI scan.

In the following cases, tumor assessment will be performed until documented PD, but it will be at the discretion of the investigator to discontinue the study treatment:

1) on-study fracture.
2) on-study management of pain (palliative radiation therapy, palliative surgery).
3) clinical worsening not objectively confirmed with X-ray, CT, or MRI scan.

It is suggested to institute palliative radiotherapy (e.g., lesions at risk for spontaneous micro-fractures or painful lesions) before study initiation as well as palliative surgery if possible and clinically appropriate.

16. Response Criteria in Solid Tumors (RECIST) 1.1

16.1 Definitions

Evaluable for Target Disease response: Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be

considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

16.2 Disease Parameters

Measurable Disease

Measurable disease
Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in ***millimeters*** (or decimal fractions of centimeters).
Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease
All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.
Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to

further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions
All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

16.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine)

The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 µCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound
Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy
The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers
Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response

Cytology, Histology
These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

16.4 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

16.5 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

16.6 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD***	Yes or No	PD
Any	Any	Yes	PD

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

17. Statistical Considerations and Analysis Plan

17.1 Overview of Study Design

This is a randomized, open-label, multicenter, Phase III trial to assess the safety and efficacy of palbociclib plus anti-HER2 therapy and endocrine therapy vs. anti-HER2 therapy plus endocrine therapy for hormone receptor positive / HER2+ metastatic breast cancer who are stable or responding after induction therapy.

This study will use a permuted block randomization to allocate an equal number of patients to each of the treatment arms. This procedure will balance the marginal distributions of the stratification factors between the treatment arms. The stratification factors that will be used are: pertuzumab use (yes vs. no), prior anti-HER2 therapy in the neo (adjuvant) setting (yes vs. no), best response to induction therapy (CR or PR vs. SD) by investigator assessment and type of endocrine therapy (fulvestrant vs. AI).

We will use an intention to treat (ITT) principle to define the population used for the analysis of the primary endpoint and secondary efficacy endpoints. The ITT Population will be comprised of all randomized patients, including those who do not start palbociclib, anti-HER2 therapy or endocrine treatment. This population provides the basis for the main efficacy analyses. Patients will be analyzed according to the treatment group to which they were randomized. Randomized patients consist of all patients who have given their written informed consent and for whom there is confirmation of successful allocation to a treatment arm.

17.2 Sample Size, Accrual Time and Study Duration

The sample size for this study is determined based on the results of a randomized Phase III trial CLEOPATRA [3] assessing trastuzumab and docetaxel with or without pertuzumab in HER2+ metastatic breast cancer in the first-line setting. The median PFS for the pertuzumab-containing

arm of the study was 18.5 months. Based upon these results and considering that the current clinical trial will enroll patients previously treated with approximately six to eight cycles of induction therapy (i.e. approximately 6 months), the median control arm in this study is assumed to be 13 months. Therefore, a risk reduction by 33% (a hazard ratio of 0.667) or an improvement by 50% to median PFS of 19.5 months with palbociclib plus anti-HER2 plus endocrine therapies is clinically significant. With one interim futility analysis planned at 50% (~135) of total PFS events and one interim efficacy analysis planned at 65% (~175) of total PFS events, a total of 269 events are required in the two arms of the study based on a 1:1 randomization to have 90% power to detect a hazard ratio of 0.667 in favor of palbociclib plus anti-HER2 plus endocrine therapies using a 1-sided, log-rank test at a significance level of 0.025. Assuming a 15% drop-out rate on either treatment arm, a non-uniform accrual [0-6 months: 10 patients per month; 6-10 months: 20 patients per month; ≥10 months: 25 patients per month] accomplished over a 24-month period and follow-up for about 12 months after the last patient is enrolled, a total sample size of 496 participants is required. No crossover to experimental therapy is permitted in the control group within the current study design.

The sample size described above will also allow the assessment of differences in the secondary endpoint of OS. The OS outcome for the pertuzumab contacting arm in the Phase 3 clinical trial (CLEOPATRA) of a similar patient population was approximately 56 months. Using similar argument as before where only 4.66% of the patients in the pertuzumab arm reported PD, allowing for ~6 months for induction treatment in the proposed trial, we assume that the median OS for the control arm in the proposed trial would be 50 months (~ 6 months less than what was reported in CLEOPATRA). Using this value as an assumption with a hypothesized 30% reduction risk (a hazard ratio of 0.70), ~10% improvement in 3 years OS probability (from 60.71% to 70.515%), or 43% improvement in median OS (from 50 months to 71.429 months) in patients randomized to receive palbociclib plus anti-HER2 plus endocrine therapies, a total of 247 events using a 1-sided, log-rank test is required for a significance level of 0.025 and power of 80% to detect the difference.

17.3 Statement for Primary Endpoint

The primary endpoint is PFS which is defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD), as defined by RECIST 1.1 criteria, or death due to any cause in the absence of documented PD, whichever occurs first. PFS data will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die while on study. Patients lacking an evaluation of tumor response after randomization will have their PFS time censored on the date of randomization with the duration of one day. Additionally, patients who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumor assessment prior to the start of the new therapy. Patients with documentation of PD after an unacceptably long interval (i.e., 2 or more incomplete or non-evaluable assessments) since the last tumor assessment will be censored at the time of last objective assessment that did not show PD for the primary analysis. Patients who report symptomatic deterioration as the only cause of PD will be censored at the date of their last tumor assessment. A sensitivity analysis for PFS will be conducted counting as events those patients who report only symptomatic deterioration as PD and patients with documentation of PD after an unacceptably long interval.

17.4 Interim Efficacy/Futility Analysis Plan

The study is designed to have one interim futility analysis, one interim efficacy analysis, and the final analysis based on the primary PFS endpoint with the investigator assessment. The Lan-DeMets/O'Brien-Fleming boundary (O'Brien et al 1979) will be used for the futility analysis. The Haybittle-Peto efficacy boundary (Haybittle 1971; Peto et al. 1976) for rejecting the null hypothesis will be used at the time of the interim efficacy analysis. To protect the integrity of the study and to preserve the type-1 error rate, a fraction of alpha (0.0002) for efficacy will be spent at the interim analysis and accounted for in the overall type I error rate. The overall significance level for the efficacy analysis of PFS will be preserved at 0.025 (1-sided test). The choice of a strict boundary ($p \leq 0.0002$) at the efficacy interim analysis was selected to provide a significant and meaningful improvement in favor of palbociclib of approximately 9 months at this point based on the assumptions. With one interim futility analysis planned at 50% (~135) of total PFS events and one interim efficacy analysis planned at 65% (~175) of total PFS events, a total of 269 events are required in the two arms of the study based on a 1:1 randomization to have 90% power to detect a hazard ratio of 0.667 in favor of palbociclib plus anti-HER2 plus endocrine therapies using a 1-sided, log-rank test at a significance level of 0.025.

17.5 Analysis Plan for Primary Efficacy Endpoint

A log-rank test (one-sided) will be used to compare PFS time between the 2 treatment arms at the interim and/or final analyses with the overall significance level preserved at 0.025 (one-sided). PFS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Median PFS time will be reported. Confidence intervals (CIs) for the PFS rate at 6 months, 1 year and 2 years will be generated. The Cox Proportional hazards model will be fit to compute the treatment hazard ratio and the corresponding 95% CI. A secondary stratified log-rank test accounting for the stratification factors will be performed and treatment hazard ratios and 95% CIs adjusted for the stratification factors will also be reported.

This study will be designed as such that only at most 20% of patients enrolled will not have received pertuzumab. We assume that the median PFS will be the same as stated above in the pertuzumab treated subgroup (13 months for the non-palbociclib treatment arm and 19.5 months for the palbociclib treatment arm). PFS outcomes will be explored within the pertuzumab receiving cohort as part of the exploratory analysis outlined in Section 17.6.8.

17.6 Secondary Clinical Endpoints

17.6.1 Blinded Independent Central Review (BICR) of Progression-free Survival

All patients who will be randomized in the study will be assessed by investigators for PFS. However, a third-party imaging core laboratory (Wright Center of Innovation in Biomedical Imaging at the University of Cincinnati) will perform BICR independent of investigator assessment on all patients. The independent third-party imaging core lab will assess clinical response and progression (determination of progression by RECIST 1.1 criteria) based on the review of scans for the study population. A sensitivity analysis for PFS using the BICR

assessments for PFS will be conducted to aid (*or meet*) Health Authorities requirements and regulatory submissions.

17.6.2 Adverse Events

Per CTEP Version 4.0 of the NCI CTCAE, an AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. All grade 2, 3, 4 or 5 AEs will be documented and assigned an attribute by treating clinician as to its relationship to treatment. For a given AE, the proportion of patients on each treatment arm who report developing a grade 2-5 of this AE will be determined.

17.6.3 Overall Survival

Overall survival (OS) is defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time will be censored to last date the patient is known to be alive.

All patients randomized will be considered evaluable for OS. OS will be hierarchically tested for significance at the time of PFS analysis, provided the primary PFS endpoint is statistically significant at the second interim and/or final analyses. If OS does not yield a significant result at the time of the second PFS interim analysis or at the time of the final PFS analysis, OS will be tested at the final OS analysis time point. The reporting of OS data will follow this procedure: OS data will not be reported until the final OS analysis unless the null hypothesis is rejected for OS at the interim testing. A log-rank test will be used to compare OS between the treatment arms. Overall type I error rate will be maintained at α=0.025 (1-sided) for the analyses of PFS and OS in this setting.

OS for the two treatment arms will be assessed using Kaplan-Meier methods and displayed graphically where appropriate. The median event times and 95% CIs will be reported. Cox regression models will be used to estimate the treatment hazard ratio and its 95% CI.
The 1-year, 2-year and 3-year survival probabilities and the corresponding 95% CIs will be estimated using the Kaplan-Meier method.

A secondary stratified log-rank test accounting for the stratification factors will be performed and treatment hazard ratios and 95% CIs adjusted for the stratification factors will also be reported.

17.6.4 Objective Response

Objective response (OR) is defined as a complete response (CR) or partial response (PR) according to RECIST v.1.1 recorded from randomization until disease progression or death due to any cause.

A patient will be considered to have achieved an OR if the patient has a CR or PR according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as non-responders in the OR rate analysis. Additionally, patients with inadequate data for tumor assessment (e.g., no baseline

assessment or no follow-up assessments) will be considered as non-responders in the OR rate analysis.

The OR rate (ORR) on each randomized treatment arm will be estimated by dividing the number of patients with OR (CR or PR) by the number of patients randomized to the respective treatment arm ("response rate"). An exact 95% binomial CI for the response rates will be provided. Response rate comparisons between the 2 treatment arms as randomized will be assessed using a chi-square test or Fisher's exact test. Analyses of ORR will be performed on the ITT population based on the investigator's assessment as well and also on the review of the blinded independent third-party core imaging laboratory.

17.6.5 Incidence of CNS Metastases

The incidence of CNS metastases will be compared between the treatment arms, which will include both the progression of existing brain metastases documented as target/non-target lesions at baseline as well as new brain metastases documented as new lesions at the time of progression on the disease assessment forms and/or patient status follow-up forms in the clinical database.

17.6.6 Duration of Response

Duration of response (DR) is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. DR data will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die due to any cause while on study. DR will only be calculated for the subgroup of patients with an OR. DR for the two treatment arms will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median event time and 95% CI for the median will be provided for each endpoint.

17.6.7 Clinical Benefit Response

Clinical benefit response (CBR) is defined as CR or PR or SD/Non-CR and Non-PD (for patients with non-measurable disease) ≥ 24 weeks according to the RECIST version 1.1 recorded in the time period between randomization and disease progression or death of any cause.

The CBR rate on each randomized treatment arm will be estimated by dividing the number of patients with CR, PR, or SD/Non-CR and Non-PD (for patients with non-measurable disease) ≥ 24 weeks by the number of patients randomized to the treatment arm. A 95% CI for the CBR rates will be provided. CBR rate comparison between the two treatment arms as randomized will be assessed using chi-square or Fisher's exact test.

17.6.8 Patient Reported Outcomes

Patient reported outcomes of health-related quality of life and health status will be assessed using validated questionnaires, the Functional Assessment of Cancer Therapy-Breast (FACT-B) and EuroQol-5D (EQ-5D). The FACT-B and EQ-5D will be given to the patient in the appropriate language for the site.

Patients will complete each instrument every 12 weeks over the course of treatment until disease progression or discontinuation of the treatment and at the end of study treatment visit.

The FACT-B consists of the FACT-G (27-items) and a breast cancer-specific scale (BCS) that consists of 10-items designed to assess patient concerns relating to breast cancer. The FACT-G is a 27-item compilation of general questions divided into 4 domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. Patients are asked to respond to a Likert scale where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much.

The FACT-B TOI-PFB is a 23-items subset of the FACT-B that can be used as a summary measure of physical and functional well-being in patients with breast cancer (Brady et al, 1997). Scores range from 0 to 92 points; a higher score indicates a better well-being. A change of 5 points in the FACT-B TOI-PFB is considered to be clinically meaningful (Brady et al 1997, Yost et al, 2005).

Change from baseline scores will also be compared between the treatment arms using a mixed model repeated measures approach adjusting for specified covariates.

Time to symptom progression is defined as time from randomization to the first documentation of ≥5-point decrease from baseline in the Trial Outcome Index-Physical/Functioning/Breast (TOI-PFB) will be a key secondary endpoint that will be compared between the two arms using survival analyses methods.

In addition, time to deterioration in breast cancer-specific (BCS) symptoms, defined by a decline in BCS from a baseline of ≥2 points will be compared between the two treatment arms as an exploratory endpoint.

Breast cancer-specific quality of life, EQ-5D index and EQ-5D VAS scores and change from baseline scores will be compared between the treatment arms using a mixed model repeated measures approach adjusting for specified covariates, including baseline.

17.6.9 Analyses for the Exploratory Objectives

In addition to the analyses specified above, PFS, OR, CBR, DR and OS will be analyzed based on the following factors: prior exposure to anti-HER2 therapy in the adjuvant/neoadjuvant setting (yes vs. no), pertuzumab use (yes vs. no); type of endocrine therapy (AI or fulvestrant) and response to induction therapy prior to study initiation (i.e. PR or CR vs. stable disease). Univariable and multivariable Cox proportional hazards models for time to event outcomes will be performed to look at the impact of baseline patient, tumor and disease characteristics.

17.7 Duration of Follow-up

Refer to Section 10.6 for follow-up information.

17.8 Criteria for Taking a Patient Off Study

Refer Section 10.5 for information on treatment discontinuation.

18. General Regulatory Considerations and Credentialing

18.1 Compliance with Trial Enrollment and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

18.2 Regulatory and Ethical Compliance

By signing the Protocol the investigator agrees to treat all of the information that is provided with the strictest confidentiality and to require the same of his/her personnel as well as the IRB. Study documents (protocols, investigator`s brochures, eCRFs, etc.) provided by the AFT will be stored in an appropriate manner in order to ensure confidentiality. The information provided to the investigator by AFT must not be made available to other parties without a direct written authorization by the aforesaid parties, with the exception of the extent to which disclosure is necessary in order to obtain informed consent from the patients who wish to participate in the study.

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulation and applicable local, state and federal laws.

By signing the study protocol the investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of good clinical practice, which these instructions and procedures reflect.

18.3 Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Informed Consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study).

In the case where the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Furthermore, it is the investigator's responsibility to obtain the signed Informed Consent Form, and a signature from the person conducting the informed consent discussion, prior to undertaking any trial-related procedure. The proposed Informed Consent Form must comply with the ICH GCP guideline and regulatory requirements.

18.4 Responsibilities of the Investigator IRB/IEC/REB

The regulatory requirements for the Investigator can be found in Subpart D of 21CFR312(21CFR 312.60: General Responsibilities of Investigators) and in ICH E6 Section 4.

Additional requirements are also outlined in the Statement of Investigator Responsibilities (Form FDA 1572) and the Site Services Agreement.
AFT, LLC will supply the protocol and subsequent amendments.

The Investigator is responsible for ensuring all patients and/or parents or legal guardian of each patient, if applicable, are informed about the study and that written consent is obtained prior to the conduct of any study related procedures.

In addition, the Investigator is responsible for reviewing all health related information collected for each study patient in order to identify any safety related issues/AE or Infusion Associated Reactions (IAR). All SAEs and IARs are to be reported within 24 hours to AFT via the AFT Safety System of becoming aware of the event. If this is not reported within 24 hours, a Protocol Deviation will be documented.

As specified in 21CFR 312.62 (Investigator Record Keeping and Record Retention) and ICH E6 Sections 4.9 and 8, the Investigator is responsible for ensuring that their study staff maintains and retains all study related documentation, including but not limited to: signed Informed Consent forms, medical records that are applicable for this study and source documents, the AFT-38 protocol, Institutional Review Board (IRB) approvals, relevant IRB and Sponsor correspondence, and assorted regulatory documents. The Investigator is responsible for retaining and keeping safe all patient related documentation. In addition, the site staff will complete electronic case report forms (eCRFs) in a timely manner.

18.5 Financial Disclosures

Investigators will provide AFT with adequate and accurate financial information in accordance with local regulations and laws in order to allow AFT to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing updated information on financial interests during the course of the study as well as for 1 year after completion of the study.

18.6 Protocol Deviations

The investigator is responsible to document and explain any deviations from the approved protocol. The investigator should promptly report any deviations that might impact patient safety and data integrity to AFT and if locally applicable, to the respective IRB in accordance with local IRB policies and procedures.

A deviation is a departure from the protocol. If deviations are discovered by the monitor or data manager, other member of study staff or otherwise, they will be discussed with the Investigator and study staff.

AFT does not provide waivers for protocol deviations.

18.7 Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by AFT, agreed by the investigator(s) and approved by relevant IRBs prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs must be provided to AFT before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the AFT, agreed by the investigator(s) and notified to the IRB.

18.8 Retention of Records (Study Documentation, Recordkeeping, and Retention of Records)

Any records and documents relating to the conduct of this study and the distribution of investigational drug, including ICFs, eCRFs, PRO data, laboratory test results, and medication inventory records, must be retained by the study chair until notification by AFT, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of AFT. Written notification should be provided to AFT prior to transferring any records to another party or moving them to another location.

18.9 Data Confidentiality

Patient medical information, whether associated with biologic specimens or not, is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. Data derived from biologic specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The overall results of any research conducted using biologic specimens will be available in accordance with the effective AFT policy on study data publication.

18.10 Database Management and Quality Control

The Site Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study.

The Medidata RAVE EDC system will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic case report form (eCRF), and transmitted in a secure manner to AFT within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF. The Clinical Research Coordinator (CRC) or designated study site personnel will complete the eCRFs in a timely manner after the information is collected, preferably within 3-5 business days after the study procedure has been performed. The Investigator will review and approve the completed eCRFs. Subjects will not be identified by name in the study database or on any study documents to be collected by the AFT (or designee), but will be identified by a unique patient number that will include a site number, subject number, and if the patient consented to participate in the MBC Initiative, a Master MBC identifier.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs.

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

AFT will review eCRFs for accuracy and completeness at regular intervals and during on-site monitoring visits; any discrepancies will be resolved with the investigator or designee, as appropriate. Data entered into the clinical study database will be verified for accuracy and consistency with the data sources according to the study specific Monitoring Plan.

Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated by the sites in accordance with the resolved queries. All changes to the study database will be documented.

At critical junctures of the protocol (e.g., production of interim and final reports), data for analysis is locked and cleaned per established procedures. At study completion, when the database has been declared to be complete and accurate, the database will be locked.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), AFT should be prospectively notified. The study records must be transferred to a designee acceptable to AFT, such as another investigator, another institution, or to AFT itself. The Investigator must obtain AFT's written permission before disposing of any records, even if retention requirements have been met.

18.11 Site Monitoring

Monitoring visits will be conducted by representatives of AFT according to the study specific Monitoring Plan and US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to AFT (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

18.12 Data and Safety Monitoring Board (DSMB)

The PATINA/AFT-38 study will utilize the AFT DSMB, an independent committee comprised of oncologists, at least one oncologist specializing in breast cancer, and an independent statistician to monitor safety and study conduct. A PATINA DSMB Charter will describe the DSMB process, including but not limited to role of the DSMB Chair, the meeting schedule, data for review during open and closed sessions, voting, and communication of recommendations.

18.13 Regulatory Reporting

SAEs meeting expedited reporting requirements (see Section 10) will be forwarded to FDA and OUS Competent Authorities by the IND Sponsor or designee within the required reporting timelines according to 21 CFR 312.32.

It is the responsibility of the investigator and the research team to ensure that SAEs are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, AFT's guidelines, and Institutional Review Board (IRB) policy.

18.14 Audits and Inspections

To enable evaluations and/or audits from regulatory authorities or AFT, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer, but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of AFT-38.

To ensure compliance with the study protocol and all local, federal and/or international regulations, sites will be audited periodically according to the study specific Audit Plan.

18.15 Early Discontinuation of the Study

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug in this patient population, e.g., study did not meet primary endpoint.

18.16 Publication of Study Protocol and Results

AFT, LLC prioritizes the timely presentation and publication of study results. Publications and any kind of presentations of results from the study shall be in accordance with accepted scientific practice, academic standards and customs and must be approved in writing by AFT as the

sponsor of this trial. No investigator may present or publish any portion of this trial without written approval from AFT.

19. References

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20. Appendices

Appendix I: ECOG Performance Status

Appendix II: Investigator Responsibilities

Appendix III: Abbreviations and Terms

Appendix IV: QOL Forms

20.1 Appendix I: ECOG Performance Status

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

20.2 Appendix II: Investigator Responsibilities

The regulatory requirements for the Investigator can be found in Subpart D of 21CFR312(21CFR 312.60: General Responsibilities of Investigators) and in ICH E6 Section 4.

Additional requirements are also outlined in the Statement of Investigator Responsibilities (Form FDA 1572) and the Site Services Agreement. AFT, LLC (AFT) will supply the protocol and subsequent amendments.

The Investigator is responsible for ensuring all patients and/or parents or legal guardian of each patient, if applicable, are informed about the study and that written consent is obtained prior to the conduct of any study related procedures.

In addition, the Investigator is responsible for reviewing all health related information collected for each study patient in order to identify any safety related issues/AE or Infusion Associated Reactions (IAR). All SAEs and IARs are to be reported to the AFT Safety Management Group within 24 hours of becoming aware of the event. If this is not reported within 24 hours, a Protocol Deviation will be documented.

As specified in 21CFR 312.62 (Investigator Record Keeping and Record Retention) and ICH E6 Sections 4.9 and 8, the Investigator is responsible for ensuring that their study staff maintains and retains all study related documentation, including but not limited to: signed Informed Consent forms, medical records that are applicable for this study and source documents, the AFT protocol, Institutional Review Board (IRB) approvals, relevant IRB and Sponsor correspondence, and assorted regulatory documents. The Investigator is responsible for retaining and keeping safe all patient related documentation. In order to do this, the site staff will complete electronic case report forms (eCRFs) in a timely manner.

20.3 Appendix III – Abbreviations and Terms

AE	Adverse Event
AI	Aromatase Inhibitor
AFT	Alliance Foundation Trials
ALT	Alanine Aminotransferases
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferases
AUC	Area Under the Curve
AUCinf	Area under the concentration-time curve from hour 0 to infinity
CAP	College of American Pathologists
CCND1	Cyclin D1
CDK	Cyclin-Dependent Kinase
ctDNA	Circulating Tumor DNA
C	Cycle
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum Plasma Concentration
CRF	Case Report Form
CSF	Colony-Stimulating Factors
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P-450
D	Day
DDI	Drug-drug interaction
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ER	Estrogen Receptor
FACT	Functional Assessment of Cancer Therapy
FDA	US Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GMP	Good Manufacturing Practice
GnRH	Gonadotropin releasing hormone
HDPE	High Density Polyethylene
HER2	Human epidermal growth factor receptor 2
HR+	Hormone receptor positive
HRQL	Health-related QOL
IB	Investigator's Brochure
IC50	Concentration of 50% Inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IIR	Investigator-Initiated Research
IP	Investigational Product; (Investigational Medicinal Product (IMP) can be used equally
IP Treatment	Palbociclib treatment within Arm A
IRB	Institutional Review Board
IUD	Intrauterine Device
IxRS	Interactive Voice and Web Response System
ITT	Intent-to-treat
LFT	Liver Function Test
LHRH	Luteinizing hormone-releasing hormone
MBC	Mastering Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OS	Overall Survival
Participant	Participant enrolled in the study; terms participant and subject can be used equally
PET	Positron Emission Tomography
PFS	Progression Free Survival
P-gp	P-glycoprotein
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetic
PPI	Proton Pump Inhibitor
PR	Partial Response or Progesterone Receptor (depending on context)
PRO	Patient Reported Outcome
Provider	Anyone rendering medical care to the patient, including e.g., physicians, nurse practitioners, physician assistants, and others.
PS	Performance Status
QD	Quaque Die (once daily)
QOL	Quality Of Life
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcS	QT interval corrected for heart rate according to a study-specific correction factor
RB/Rb	Retinoblastoma
RNA	Ribonucleic Acid
RR	The interval between an R wave and the next R wave
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Stable Disease or Standard Deviation (depending on context)
SmPC	Summary of Product Characteristics
SULT	Sulfotransferase
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tmax	Time for Cmax
ULN	Upper Limit of Normal
US	United States
USA	United States of America
Vz/F	Apparent Volume of Distribution
WBC	White Blood Cells

20.4 Appendix IV: Quality of Life Forms

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐