Cancer Research Consortium of West Michigan
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FAST FACTS

AFT -38 – Patina - 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

CRCWM patients will not be asked to consent to any research only biopsies as indicated in the protocol. All references to optional [research only] biopsies have been removed from our local consent forms. Patients may opt to submit tissue specimens for research only when biopsies are performed as part of routine care.

Inclusion Criteria (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.

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:
    a. Disease outside the CNS is present.
    b. No evidence of interim progression between the completion of induction therapy and the screening radiographic study.
    c. No history of intracranial hemorrhage or spinal cord hemorrhage
    d. Not requiring anti-convulsants for symptomatic control
    e. 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

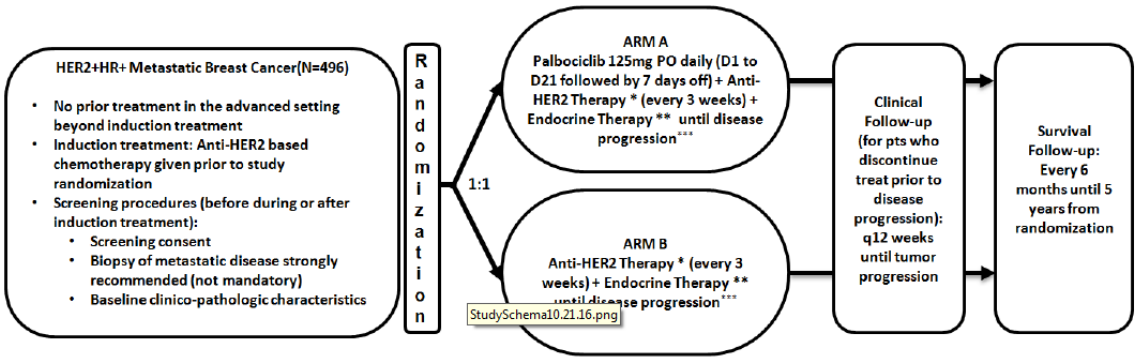
Baseline Body Function Specifics

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

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.