Study Synopsis NA-PHER2/ FM-14-B01

TITLE	*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*
PROTOCOL VERSION	Protocol Version 3.0 ï March, 2016
SPONSOR	Fondazione Michelangelo
PROTOCOL PHASE	Exploratory Phase II with parallel cohorts
TRIAL CONDUCT	This is a multicenter neoadiuvant trial conducted under the sponsorship and overall trial management of the Fondazione Michelangelo in Italy
INDICATION	Women with a diagnosis of invasive unilateral non metastatic ER-positive breast cancer expressing HER2 and suitable for neoadjuvant therapy
STUDY DESIGN **AND TREATMENT PLAN**	Open-label neoadjuvant trial for women with early and locally advanced untreated breast cancer Three cohorts of patients are planned <u>Patients with ER positive tumors (> 10%) and HER2 3+ or neu amplified</u> *Cohort A* Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF) *Cohort B* Trastuzumab+Pertuzumab+Palbociclib (HPP) ***Allocation to Cohort B will be started after recruitment to Cohort A has been completed*** <u>Patients with ER positive tumors (> 10%), PgR positive, HER2 1+/2+ (without amplification) and Ki67 > 20%</u> *Cohort C* Trastuzumab+Pertuzumab+Palbociclib+Fulvestrant (HPPF) Treatment Schedule Trastuzumab 8 mg/kg loading dose IV, then 6 mg/kg IV q.3 wks (repeat for a total of 6 administrations) Pertuzumab 840 mg loading dose IV, then 420 mg IV q. 3 wks (repeat for a total of 6 administrations) Palbociclib 125 mg po q.d. x 21 q. 4 wks (= 1 cycle; repeat for a total of 5 cycles) Fulvestrant will be given intra-muscle at the dose of 500 mg every 4 weeks (repeat for 5 times) with an additional 500 mg dose given two weeks after the initial dose (total administrations including the additional one = 6) The total duration of neoadjuvant palbociclib (5 cycles every 4 weeks) and fulvestrant (5 administrations every 4 weeks plus the additional dose given two weeks after the initial dose) was selected to match as closely as possible the total duration of the

	six planned 3-weekly administrations of trastuzumab and pertuzumab Definitive surgery will be performed not earlier than 14 days and not later than 28 days after the last dose of any of the drugs in the combination reported above After completion of the neoadjuvant and surgical treatment patients will receive irradiation as locally acceptable. Patients will also continue to receive systemic drug therapy including chemotherapy (plus standard anti-HER2 treatment until completion of full 1 year if HER2 3+ or neu amplified, i.e. cohorts A and B) and endocrine therapy according to local guidelines at the Investigatorôs discretion.
OBJECTIVES	***Primary objectives*** Each cohort will be assessed separately for • Characterization of Ki67 changes from baseline before therapy and at 2 weeks and at surgery (approximately 22 weeks after start of neoadjuvant therapy) • Characterization of changes in apoptosis from baseline before therapy and at surgery (approximately 22 weeks after start of neoadjuvant therapy) • Study the tolerability profile of the combination ***Secondary objectives*** Each cohort will be assessed separately for • Rate of pathological complete response (pCR) defined as absence of invasive cells in breast and axilla (ypT0-ypTis ypN0) at surgery • Clinical objective response rate at the end of the combination • Conduct molecular and clinical analyses to assess the presence of informative markers of benefit in addition to Ki67 and apoptosis
ELIGIBILITY CRITERIA	**Inclusion Criteria** Patients must meet ALL of the following criteria in order to be eligible for this study: 1. Female patients aged 18 years or older with tumors suitable for neoadjuvant treatment 2. Early (> 1.5 cm) or locally advanced untreated breast cancer 3. Histologically confirmed invasive unilateral breast cancer 4. HER2 status to be centrally confirmed (HER2 3+ of neu amplified for cohorts A and B; HER2 1+/2+ without amplification for cohort C)

	5. Positive estrogen receptor (ER) > 10% and known progesterone receptor (PgR). Note: PgR assessment must be positive for cohort C 6. Ki67 > 20% for cohort C 7. Available paraffin-embedded tumor block taken at diagnostic biopsy for central retrospective confirmation of HER2 and ER eligibility and for assessment of Ki67 value and apoptosis is mandatory 8. All patients must agree to provide tumor tissues for centralized assessment of KI67 values and apoptosis at the required timelines (2 weeks from starting protocol therapy and at surgery) 9. ECOG performance status 0 or 1 10. Written informed consent to participate in the trial (approved by the Institutional Review Board [IRB]/ Independent Ethics Committee [IEC]) obtained prior to any study specific screening procedures 11. Willing and able to comply with the protocol **Exclusion Criteria** Patients meeting any ONE of the following criteria are not eligible for this study: 1. Evidence of bilateral invasive breast cancer or metastatic disease (M1) 2. Pregnant or lactating women. Documentation of a negative serum pregnancy test must be available for premenopausal women with intact reproductive organs and for women less than one year after the last menstrual cycle **3.** Women with childbearing potential unless (1) surgically sterile or (2) using adequate measures of contraception, for example abstinence, an intra-uterine device, or double barrier method of contraception up to 7 months from the last dose of either anticancer study drug 4. Previous treatment with chemotherapy, hormonal therapy or an investigational drug for any type of malignancy 5. Previous extensive radiotherapy 6. Previous investigational treatment for any condition within 4 weeks of registration date 7. Known hypersensitivity reaction to one of the compounds or incorporated substances used in this protocol 8. Previous or concomitant malignancy of any other type that could affect compliance with the protocol or interpretation of results. Patients with curatively treated basal cell carcinoma of the skin, stage 1 uterine cancer or in situ cervix cancer are generally eligible. 9. Other serious illness or medical condition including: history of documented congestive cardiac failure; angina pectoris requiring anti-anginal medication; evidence of transmural infarction on ECG; poorly controlled hypertension (e.g. systolic >180 mm Hg or diastolic >100 mm Hg; however, patients with hypertension which is well controlled on medication are eligible); clinically significant valvular heart disease; high-risk uncontrolled arrhythmias

	10. Baseline left ventricular ejection fraction (LVEF) < 55% by echocardiography or multi-gated scintigraphic scan (MUGA) 11. QTc >480 msec or a family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP) 12. Patients with a history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant and precluding informed consent or adversely affecting compliance with study drugs 13. Serious uncontrolled infections (bacterial or viral) or poorly controlled diabetes mellitus 14. Current use or anticipated need for food or drugs that are known strong CYP3A4 inhibitors or inducers 15. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia) 16. Any of the following abnormal baseline hematological values: a. Absolute Neutrophil Count (ANC) < 1.5×10^9/L b. Platelet count < 100×10^9/L c. Hemoglobin (Hb) < 10 g/dL 17. Any of the following abnormal baseline laboratory tests a. Serum total bilirubin > 1.5 × ULN (upper limit of normal) (except for patients with clearly documented Gilbert's syndrome) b. Alanine transaminase (ALT) or aspartate transaminase (AST) > 1.25 × ULN c. Alkaline phosphatase > 2.5× ULN d. Serum creatinine > 1.5 × ULN e. INR > 2
ASSESSMENT OF - **Changes of Ki67 and in apoptosis** - **Safety**	***Changes in Ki67 levels*** will be measured from baseline before therapy and at 2 weeks and at surgery (approximately 22 weeks after start of neoadjuvant therapy with HPPF). Changes will be assessed on core-cut tumor biopsies taken at the above times using a 14-gauge needle from the primary breast fixed in neutral buffered formalin and embedded in paraffin wax ***Changes in apoptosis*** will be measured from baseline before therapy and at surgery (approximately 22 weeks after start of neoadjuvant therapy with HPPF). Changes will be assessed on core-cut tumor biopsies taken at the above times using a 14-gauge needle from the primary breast fixed in neutral buffered formalin and embedded in paraffin wax ***Safety*** Patients will be assessed for adverse events by clinical examination, questioning for symptoms of toxicity, laboratory assessments, vital signs, ECG and LVEF. All adverse events will be assessed throughout the study according the National Cancer

	Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) Version 4.03.
DURATION AND NUMEROSITY OF THE STUDY	Recruitment will occur during a 12 months period from first patient in (FPI) in each cohort of patients. The end of the study is defined as the date when the last patient, last visit [LPLV (28-35 days after definitive surgery, i.e. end of protocol therapy, or 28-35 days after the last dose of medical treatment if surgery is not performed for any reason)] occurs and it is expected approximately 7 months after the last evaluable patient per cohort is registered into the study. We plan to enroll a minimum of 32 patients per cohort in order to have 25 cases per cohort with fully adequate sampling of pre-study, week-2 and surgical tumor specimens for the assessment of the primary endpoint. Due to the exploratory nature of the design, this sample size was based on feasibility and accrual constraints rather than on formal statistical criteria. The study can be terminated at any time for safety reasons (i.e. adverse events, high rate of disease progression during neoadjuvant therapy, high rate of consent withdrawal) or slow accrual.