NCT02626507

IRB Approved at the
Protocol Level
Dec 31, 2018

CLINICAL STUDY PROTOCOL

Phase I Dose-Escalation Study of Combination of Gedatolisib (a Dual Inhibitor of PI3-K and mTOR) with Palbociclib and Faslodex in the Neoadjuvant Setting in Previously Untreated Patients with ER+/HER2- Breast Cancer

Protocol Number: CL-Gedatolisib-001

Investigational Drug: Gedatolisib (Code name PF-05212384, formerly known as PKI-587)

US IND Number: 128,914

Sponsor: Anthony Hoffman, MD
Hoffman Oncology
1461 Astor Avenue
Bronx, NY 10469

Medical Monitor: Anthony Hoffman, MD (718-655-1005)

Current Version: October 2018

Previous Versions: May 2018
January 2017
May 2016
February 2016
January 2016, V2
January 2016
December 2015 (Amendment 0)

STUDY SYNOPSIS

Study Title (Study No.)	Phase I Dose-Escalation Study of Combination of Gedatolisib (a Dual Inhibitor of PI3-K and mTOR) with Palbociclib and Faslodex in the Neoadjuvant Setting in Previously Untreated Patients with ER+/HER2- Breast Cancer (CL-Gedatolisib-001)
Study Objectives	The primary objectives of the current study are: - Safety, tolerability and potential efficacy of Gedatolisib when used in combination with palbociclib and Faslodex (fulvestrant), administered in the neoadjuvant setting in previously untreated patients with ER+/HER2- breast cancer. - The MTD of Gedatolisib when used in combination with palbociclib and Faslodex in these patients. The secondary objective of the current study is: - pCR induced by the Gedatolisib/palbociclib/Faslodex combination in the neoadjuvant setting in previously untreated patients with ER+/HER2- breast cancer. The exploratory objectives of the current study are: - To assess the baseline values, and potential correlations between the baseline values and their response to the investigational neoadjuvant therapy, of the genomic test Foundation CDx™ in tumor tissue and the genomic test FoundationOne®Liquid in peripheral whole blood.
Study Drug	Gedatolisib (Code name PF-05212384, formerly known as PKI-587)
Study Design	Dose-Escalation, Open-Label and Non-Randomization: This is a dose-escalation Phase Ib clinical trial in 18 patients with newly diagnosed Stage II-III ER+/HER2- breast cancer, with the primary cancer in place. These patients have not received prior therapy for their breast cancer and are intended to undergo surgery after four cycles of therapy. This is an open-label study, and investigators and subjects are not blinded to the treatment. An open-label study design is used because this is a dose-escalation trial and the investigators need to determine the potential toxicity before a decision can be made to continue the dose escalation procedures. The assignment of patients will not be randomized, as this is a dose-escalation trial. Duration of Treatment, Treatment Cycle and Study Drug Administration: Each patient will be treated for a total of four treatment cycles. Each treatment cycle is four weeks or 28 days. During each treatment cycle, Gedatolisib, Palbociclib, Faslodex and, in pre-menopausal patients, Zoladex, Eligard or Lupron Depot, are given as outlined in Table A (next page).

- Cont'd on the next page –

STUDY SYNOPSIS (cont'd)

Study Design (cont'd)

Table A: Treatment with Gedatolisib, Palbociclib and Faslodex for Four 4-Week Treatment Cycles

Patient Type	Drugs	Dose Per Administration	Route and Administration	Dosing Regimen
Pre- and Post-Menopausal Subjects	Gedatolisib	150, 180*, 215 or 260 mg	IV, over 30 minutes	Once weekly for each of the four 4-week cycles.
	Palbociclib	125 mg	PO, with food	Once daily on Days 1-21 for each of the four 4-week cycles.
	Faslodex	500 mg	IM, into the buttocks slowly over 1-2 minutes per injection as two 5-mL injections, one in each buttock.	Once daily on Days 1 and 15 of Cycle 1, and on Day 1 of each of the remaining three 4-week cycles.
Pre-Menopausal Subjects Only (use any one of the three drugs shown)	Zoladex	3.6 mg	SC, into the anterior abdominal wall below the navel line using an aseptic technique under the supervision of a physician.	Once every 28 days, starting 1 week prior to treatment.
	Eligard	7.5 mg	SC, into the abdomen, upper buttocks, or another location with adequate area not having excessive pigment, nodules, lesions, or hair, and choose an area that hasn't recently been used. Use an aseptic technique according to the instructions stated in the Package Insert and under the supervision of a physician.	Once monthly, starting 1 week prior to treatment.
	Lupron Depot	7.5 mg	IM, using an aseptic technique according to the instructions stated in the Package Insert and under the supervision of a physician.	Once monthly, starting 1 week prior to treatment.

DLT = dose-limiting toxicity; IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous.

* 180 mg is the starting dose in this dose-escalation study. If DLT is observed in two or more patients in the first cohort at the dose level of 180 mg, the dose will be de-escalated with the dose of the next cohort reduced to 150 mg.

Dose Escalation and De-Escalation Scheme of Gedatolisib:

Dose Escalation Scheme: Gedatolisib is administered by IV once weekly during the four 4-week cycles, for a total of 16 weeks. The dose will be escalated in three cohorts, at dose levels of 180 mg, 215 mg and 260 mg. The number of patients in each cohort will initially be three. If no patients in any cohort develop a dose-limiting toxicity (DLT, defined below), dose escalation will continue in cohorts of three patients. However, if a DLT is observed in a patient (whether it is the first, second or third of the three intended patients) at any dose level, the cohort of that dose level will be expanded to a maximum of six patients. If no DLT is observed in another patient out of a maximum of six patients, dose escalation procedure will continue in three patients for each subsequent cohort. However, once a DLT is observed in a total of two patients in any cohort, dosing of Gedatolisib in patients at that dose level will stop immediately, even though the total number of patients at the last cohort may be as few as two. Dose escalation is considered to be complete. The dose level that induces a DLT in two or more patients is considered to be above MTD, and the dose level immediately below the dose level that induced a DLT in two or more patients is considered the MTD. Once the MTD has been determined, additional patients will be treated with Gedatolisib at MTD so that a total of 18 patients are treated in this trial.

Dose De-Escalation Scheme: If DLT is observed in two or more patients in the first cohort at the dose level of 180 mg, the dose for the next cohort will be reduced to 150 mg. If DLT is also observed in two or more patients at 150 mg, the study will be discontinued and patients will proceed with standard of care treatment for breast cancer. If DLT is observed in less than two patients at 150 mg, 150 mg is considered the MTD. Once the MTD has been determined, additional patients will be treated with Gedatolisib at MTD so that a total of 18 patients are treated in this trial.

- Cont'd on the next page –

- Cont'd from the previous page -

STUDY SYNOPSIS (cont'd)

Study Design (cont'd)

Definition of DLT: A DLT is defined as the occurrence of any clinically relevant, grade ≥3 according National Cancer Institute (NCI) Common Toxicity Criteria (CTC), non-hematologic, non-infectious toxicity. The following toxicities are excluded from defining a DLT: Grade 3 nausea and vomiting responsive to anti-emetics, Grade 3 diarrhea responsive to anti-diarrheal therapy, Grade 3 tumor lysis syndrome, Grade 3 or 4 metabolic derangements attributed to tumor lysis syndrome or antimicrobial medications that correct with oral or IV supplementation. A DLT is also defined as the occurrence of Grade 3 thrombocytopenia with clinically significant bleeding (i.e., requires hospitalization, transfusion of blood products, or other urgent medical intervention); Grade 4 thrombocytopenia; ≥ Grade 3 febrile neutropenia (absolute neutrophil count $<1.0\times10^9$/L and fever > 101°F/38.3°C); Grade 4 neutropenia that does not recover to Grade ≤2 in ≤3 days after interrupting study drug; or Grade 4 anemia not explained by underlying disease or some other concomitant disorder.

When Dose Escalation Can Take Place: Dose escalation to the next dose level cannot take place until all patients at the previous cohort have been given a complete cycle of treatment (i.e., 4 weeks).

Intra-Patient Dose Escalation Not Used: Intra-patient dose escalation is not allowed. Each patient can only participate in a single cohort.

Dose Delay and Dose Modification in the Event of Adverse Events

Dosing Delay and Dose Modification for Adverse Events Related to Gedatolisib and Palbociclib: Gedatolisib and Palbociclib dose modifications for treatment-related toxicities requiring treatment interruption/delay despite optimal medical treatment are described below. The possible dose levels of Gedatolisib are shown in Table B (below). For Palbociclib, the dose to be used is 125 mg. First dose reduction is to 100 mg, second dose reduction is to 75 mg.

Table B: Modification of Gedatolisib Dose for Gedatolisib Related Toxicities.

If the Gedatolisib Dose is:	Available Dose of Gedatolisib for Dose Modification Due to Adverse Event		
	DL-1	DL-2	DL-3
150 mg	140 mg	130 mg	120 mg
180 mg	150 mg	140 mg	130 mg
215 mg	180 mg	150 mg	140 mg
260 mg	215 mg	180 mg	150 mg

NA = Not Applicable; DL-1 = first dose reduction; DL-2 = second dose reduction; DL-3 = third dose reduction.

Hematologic Toxicities:

- If Grade 1 or 2, then no dose modification is required.
- If Grade 3 or 4 then see below for modifications of Gedatolisib and Palbociclib:

  Gedatolisib:
  - Withhold dose until toxicity is Grade ≤2, then resume treatment at *next lower dose*. (**Note:** If the toxicity reoccurs with Grade 4 severity, withhold dose until toxicity is Grade ≤2, and then resume treatment at the same dose level or discontinue protocol directed therapy at the discretion of the Investigator.)

  Palbociclib:
  - Withhold Palbociclib, repeat complete blood count monitoring within 1 week.
    - If recovered to Grade ≤2, resume at the *same dose*.
    - If Grade 3, hold until recovery to Grade ≤2. Resume at the *same dose*.
    - If Grade 4, hold initiation of next cycle until recovery to Grade ≤2. Resume at the *next lower dose*.
    - Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles.

- Cont'd on the next page –

- Cont'd from the previous page -

STUDY SYNOPSIS (cont'd)

Study Design (cont'd)	**Non-Hematologic Toxicities:** - If Grade 1 or 2, no dose modification is required. - If Grade ≥ 3 (including, nausea, vomiting, diarrhea, and hypertension, and only if persisting despite optimal medical treatment), then: o Withhold dose of Gedatolisib and Palbociclib until toxicity is Grade ≤ 2, then resume treatment at *next lower dose of each agent*. o If the toxicity recurs with Grade 3 severity, withhold dose of Gedatolisib and Palbociclib until toxicity is Grade ≤2 and then resume treatment at the *next lower dose of each agent* or discontinue protocol directed therapy.* **Gastrointestinal toxicities** - If Grade 1 or 2, no dose modification is required. - If Grade ≥3 nausea/vomiting despite optimal antiemetic treatment, Grade 3 mucositis, or Grade 3 diarrhea despite optimal anti-diarrheal treatment, then: o Withhold dose of Gedatolisib and Palbociclib until toxicity is Grade ≤2, then resume treatment at *next lower dose of each agent*. o If the toxicity reoccurs with Grade 3 severity, despite optimal supportive care, withhold dose of Gedatolisib and Palbociclib until toxicity is Grade ≤ 2, and then resume treatment at *next lower dose of each agent* or discontinue treatment at the discretion of the Investigator. o Grade 4 diarrhea/mucositis, discontinue protocol directed therapy.* **Metabolic toxicities** - If Grade 1, no dose modification is required. - If Grade ≥2 hyperglycemia, implement hyperglycemia management. No dose modification is required. - If Grade 4 hyperglycemia despite optimal anti-hyperglycemic treatment, discontinue protocol directed therapy.* **Pneumonitis** - If Grade 1, no dose modification is required. Initiate appropriate therapy. - If Grade 2, consider interruption of therapy with Gedatolisib and Palbociclib: o Initiate clinically appropriate monitoring. o Reduce at *next lower dose of each agent*. o If Grade ≥ 2 toxicity recurs discontinue protocol directed therapy.* - If Grade 3, discontinue protocol directed therapy. **Failure to recover** - Patients must discontinue protocol directed therapy* after failure to recover to Grade ≤1 or baseline severity for drug-related toxicity (or, at the Investigator's discretion, Grade ≤2 for toxicities not considered a safety risk for the patient) after delaying initiation of the next cycle by a maximum of 2 weeks. * At discontinuation of therapy, operable patients should proceed promptly to surgery. *Dosing Delay and Dose Modification for Adverse Events Related to Faslodex*: For adverse events that are possibly related to faslodex, the dose modification procedures stated in the Package Inserts of these drugs will be followed.

- Cont'd on the next page –

- Cont'd from the previous page -

STUDY SYNOPSIS (cont'd)

Inclusion/ Exclusion Criteria	Inclusion Criteria: Patients must meet all inclusion criteria before enrollment: A. Stage II-III, with primary cancer in place, non-inflammatory invasive breast cancer confirmed by core needle or incisional biopsy (excisional biopsy is not allowed): - the disease is ER+ (defined as ER expression ≥1% of invasive cancer cells according to immunohistochemical [IHC] staining) - HER2- (defined as IHC staining of 0 to 1+ or fluorescence *in situ* hybridization [FISH] ratio of HER2 gene copy/chromosome 17 of <2.0.) - patient's disease is previously untreated for breast cancer, operable and patient intends to undergo surgery for her disease (e.g., a mastectomy or lumpectomy) after completion of neoadjuvant therapy - the disease must be with palpable or clinically assessable tumors in the breast - the disease must be radiographically measurable in the breast (Radiographically measurable disease is defined as longest diameter ≥10 mm (1.0 cm) - the disease cannot be axillary disease only (i.e., no identifiable tumor in the breast that is ≥1 cm on physical exam or radiographic study) - the disease can be multi-centric or bilateral disease, provided one target lesion meets the above eligibility criteria - breast cancer patients with lobular and luminal histology will be included. However, patients with lobular histology should not be more than a quarter of the total number of patients in this trial, as the investigational drugs are likely to have greater activities in patients with luminal histology. (**Note:** In patients with Stage III disease, PET/CT imaging studies is performed to rule out overt metastatic disease. In patients with clinically positive axillae, histologic confirmation by biopsy or fine-needle aspiration is performed. Patients with clinically negative axillae can undergo pretreatment sentinel lymph node sampling.) B. Females ≥18 years of age. C. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use effective contraceptive methods (such as abstinence, intrauterine device [IUD], or double barrier device) during the study and for at least 3 months following completion of the study, and must have a negative serum or urine pregnancy test within 2 weeks prior to treatment initiation. D. Mentally competent, able to understand and willingness to sign the informed consent form. E. At least 4 weeks must have elapsed from any prior major surgery or hormonal therapy. The following procedures are not considered major surgical procedures: - Obtaining the required research h needle biopsies - Placement of a radiopaque clip to localize a tumor or tumors for subsequent surgical resection - Placement of a port for central venous access - Fine needle aspiration of a prominent or suspicious axillary lymph node - Needle biopsy of a clinically or radiographically detected lesion to rule out metastatic disease - Sampling of sentinel lymph node F. Laboratory values ≤2 weeks must be: - Adequate glycemic balance (hemoglobin A1c or glycated hemoglobin ≤8%; fasting serum glucose ≤130 mg/dL, and fasting triglycerides ≤300 mg/dL). - Adequate hematology (white blood cell [WBC] ≥3500 cells/mm^3 or ≥3.5 bil/L; Granulocytes ≥ 1,000/μL; platelet count ≥100,000 cells/mm^3 or ≥100 bil/L; absolute neutrophil count [ANC] ≥1500 cells/mm^3 or ≥1.5 bil/L; and hemoglobin (Hgb) ≥9 g/dL or ≥90 g/L). - Adequate hepatic function (aspartate aminotransferase ≤3x upper normal limit [UNL], alanine aminotransferase ≤3x UNL, bilirubin ≤1.5x UNL).- Adequate renal function (serum creatinine ≤1.5 mg/dL or 133 μmol/L). - Adequate coagulation (International Normalized Ratio [INR] must be ≤1.5)

- Cont'd on the next page –

- Cont'd from the previous page -

STUDY SYNOPSIS (cont'd)

Inclusion/ Exclusion Criteria (cont'd)	Exclusion Criteria: Patients with any of the following characteristics will be excluded: A. Serious medical illness, such as significant cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, symptomatic coronary artery disease, myocardial infarction within the past 6 months, uncontrolled or symptomatic cardiac arrhythmia, or New York Heart Association Class III or IV), or severe debilitating pulmonary disease, that would potentially increase patients' risk for toxicity B. A marked baseline prolongation of QT/QTc interval (e.g., repeated exhibition of a QTc interval >470 ms). C. A history of additional risk factors for torsade de pointes (e.g., clinically significant heart failure, hypokalemia, family history of Long QT Syndrome). D. Arterial thrombotic event, stroke, or transient ischemia attack within the past 12 months E. Uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg), or peripheral vascular disease ≥grade 2 F. Active central nervous system (CNS), epidural tumor or metastasis, or brain metastasis. G. Any active uncontrolled bleeding, a bleeding diathesis (e.g., active peptic ulcer disease), or a history of bleeding (e.g., hemoptysis, upper or lower gastrointestinal bleeding) within the past 6 months H. Dyspnea with minimal to moderate exertion. Patients with large and recurrent pleural or peritoneal effusions requiring frequent drainage (e.g. weekly). Patients with any amount of clinically significant pericardial effusion. I. Diabetes of any type, except non-insulin dependent diabetes mellitus (NIDDM) that is controlled and with hemoglobin A1c ≤8%. J. Evidence of active infection during screening, or serious infection within the past month K. Patients with known HIV infection. L. Serious or non-healing wound, skin ulcer, or bone fracture M. Abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months N. Neuropathy of grade ≥2 O. Albumin <2.5 g/dL or <25 g/L. P. Lactating females. Q. Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients. R. Unwilling or unable to follow protocol requirements. S. Patients receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any indication within the past 3 weeks prior to participating in the study. T. Requirement for immediate palliative treatment of any kind including surgery and radiation.
Study Procedures	The study procedures are outlined in Table C (next page).

- Cont'd on the next page –

STUDY SYNOPSIS (cont'd)

Table C: Procedures for Treatment with Gedatolisib, Palbociclib and Faslodex in Each of the Four 4-Week Treatment Cycles

Treatments and Assessments	Screening [b]	Each 4-Week Treatment Cycle																											Surgery [l]
		Days on Week 1							Days on Week 2							Days on Week 3							Days on Week 4							
		1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	
Treatments:																														
Gedatolisib		√							√							√							√							
Palbociclib		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√								
Faslodex		√														√[a]														
Zoladex, Eligard or Lupron Depot (pre-menopausal patients only)	Once every 28 days, starting 1 week prior to treatment.																													
Medical history & current medication	√																													
Cancer history [c]	√																													
Hemioglobin A1c	√																													√ [k]
ECG	√ [i]																													
Physical exam and body weight	√ [d]	√ [d]							√ [d]							√ [d]							√ [d]							
Vital signs and evaluation of symptoms	√ [e]	√ [e]							√ [e]							√ [e]							√ [e]							√ [k]
Pregnancy test for woman of child-bearing potential	√ [f]																													
Safety Assessments:																														
- Fasting serum glucose and fasting triglycerides, as well as insulin, C-peptide and cholesterol	√ [g]	√ [g]																												√ [k]
- Clinical chemistry, hematology & coagulation	√ [g]	√ [g]							√ [g]							√ [g]							√ [g]							√ [k]
Tumor Response Assessments:																														
- Radiographic tumor response assessments	√ [m]																													√ [m]
- Clinical tumor response assessments	√ [n]																												√ [n]	
Efficacy and Biomarkers/Genomics:																														
- Tumor Tissues: pCR/pCR background information and Foundation CDx™	√ [h]																													√ [h]
- Blood: FoundationOne®Liquid	√ [j]																													√ [j]

pCR = pathological complete response; WBC = white blood cells.

[a] Dosing on Days 1 and 15 takes places only in Cycle 1. Dosing in the remaining three 4-week cycles takes place on Day 1 only.

[b] Screening includes medical history; current medications; cancer history; physical exam; body weight; height (screening only); vital signs; evaluation of symptoms; and blood work (clinical chemistry, hematology and coagulation). Screening must be performed within two weeks prior to neoadjuvant treatment, except that radiographic tumor response assessments can be performed within 4 weeks prior to neoadjuvant treatment.

[c] Cancer history includes: date of diagnosis, current stage of disease, date of diagnosis of the current stage of disease, and cancer-related treatment history.

[d] Physical exam and body weight will be performed during screening and immediately before Gedatolisib administration. They can be performed whenever clinically indicated. Height will also be assessed during screening.

[e] Vital signs and evaluation of symptoms will be performed during screening, immediately before Gedatolisib administration, and immediately after Gedatolisib administration. They can also be performed whenever clinically indicated.

[f] Obtain within 2 weeks prior to treatment initiation. Also performed at least monthly in pre-menopausal women.

[g] Blood work (clinical chemistry, hematology and coagulation), as well as fasting serum glucose, fasting triglycerides, insulin, C-peptide and cholesterol are assessed in the clinic. Blood work will be performed at baseline, weekly and before surgery. During neoadjuvant therapy, blood work is to be performed with results available for review within 72 hours prior to the start of treatment each week. Fasting serum glucose is performed at baseline and on Day 1 of each of the four treatment cycles during neoadjuvant therapy; fasting triglycerides are performed at baseline; whereas insulin, C-peptide and cholesterol are performed at baseline and before surgery. For fasting serum glucose and fasting triglycerides, patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment). For tests that are required before the first dose of Cycle 1, the results from screening can be used.

[h] Tumor tissues are obtained at baseline via needle biopsy,and post-treatment from tumor excision surgery to assess pCR (pCR background information at baseline) and genomics via the Foundation CDx™ test. Extra tumor samples, if available, are stored for possible future testing.

[i] ECG is assessed at screening to exclude subjects with a marked prolongation of QT/QTc interval (e.g., repeated exhibition of a QTc interval >470 ms).

[j] Whole blood samples are obtained at baseline, post-treatment (before tumor excision surgery), and at the first follow up visit after surgery for assessment of genomics via the FoundationOne®Liquid test. Extra blood samples, if available, are stored in sample tubes from the sample kits provided by FoundationOne for possible future testing.

[k] To be performed before surgery to ensure vital signs, symptoms and lab values are back to normal prior to surgery. Surgery can be performed with total WBC >3,000 cells/mm^3.

[l] Surgery should be performed 3 weeks after completion of neoadjuvant therapy. If surgery is delayed, the actual time of surgery in reference to completion of neoadjuvant therapy is to be recorded and the reason for delay (e.g., recovery from adverse effects from neoadjuvant therapy) should be documented.

[m] Radiographic tumor response assessments are performed at baseline, and after 2 cycles of neoadjuvant therapy (performed on Week 4 of Cycle 2 after completion of study drug administration) using the same imaging modality used to obtain baseline tumor measurements. If there is radiological evidence of disease progression, patients should be withdrawn from study and operable patients should proceed promptly to surgery.

[n] Clinical tumor response assessments with physical exam of the breast and axilla are performed at baseline, and at the end of each cycle during Week 4 or on Day 1 prior to the start of treatment of the next cycle. Patients with Stage II-III disease who demonstrate clinical evidence of disease progression should be withdrawn from study and operable patients should proceed promptly to surgery.