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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

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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).

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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.

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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.

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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.

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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)

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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).

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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.

TABLE OF CONTENTS

Abbreviations

AC = ante clbum (before meals)
AE = adverse events
ADR = adverse drug reactions
AJCC = American Joint Committee on Cancer
ALT = alanine aminotransferase
ALP = alkaline phosphatase
ANC = absolute neutrophil count
ASCO = American Society of Clinical Oncology
AST = aspartate aminotransferase
ATP = Adenosine triphosphate
BUN = blood urea nitrogen
CBC = complete blood counts
CDK = cyclin-dependent kinase
CDx = companion diagnostic
CFR = Code of Federal Regulations
CNB = Core Needle Biopsy
CNS = central nervous system
CRF = case report form
CTC = common toxicity criteria
DFS = disease-free survival
DLT = dose-limiting toxicity
DM = Diabetes Mellitus
ER+ = estrogen receptor positive
FBG = fasting blood glucose
FDA = Food and Drug Administration
FFPE = Formalin-fixed, paraffin-embedded
FISH = fluorescence *in situ* hybridization
GCP = Good Clinical Practices
G-CSF = granulocyte colony stimulating factor
HER2- = human epidermal growth factor receptor 2 negative
Hgb = hemoglobin
IHC = immunohistochemical
IM = intramuscular or intramuscularly
IND = Investigational New Drug
INR = International Normalized Ratio
IRB = Institutional Review Board
IUD = intrauterine device
IV = intravenous or intravenously
LDH = lactate dehydrogenase

MEK	= MAPK/ERK kinase
MSI	- microsatellite instability
mTOR	= mammalian target of rapamycin
MTD	= maximum tolerated dose
NCI	= National Cancer Institute
NIDDM	= non-insulin dependent diabetes mellitus
p-*Akt*	= phosphorylated *Akt*
PCA	= patient controlled analgesia
pCR	= pathological Complete Response
PFS	= progression-free survival
PI3-K	= phosphatidylinositol-4,5-bisphosphate 3-kinase
PIK3CA	= phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PO	= oral or orally
QD	= once daily
RPPA	= Reverse-Phase Protein Array
RSA	= Research Study Assistant
SC	= subcutaneous or subcutaneously
SAE	= serious adverse event
SGOT	= serum glutamic-oxaloacetic transaminase
SGPT	= serum glutamic-pyruvic transaminase
TLS	= tumor lysis syndrome
TMB	= tumor mutational burden
UNL	= upper normal limit
WBC	= white blood cell

1. BACKGROUND, STUDY RATIONALE AND STUDY OBJECTIVES

1.1 Background and Study Rationale

Palbociclib (Ibrance®) is an orally active highly selective reversible inhibitor of cyclin-dependent kinase (CDK) 4 and CDK 6. Faslodex® (Fulvestrant) is a potent anti-estrogen drug that binds and degrades estrogen receptors (ERs). Interim results from the Phase 3 trial (Study PALOMA-3) have shown that combination of palbociclib and Faslodex increases progressive-free survival (PFS) from 3.8 to 9.2 months in patients with metastatic estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) breast cancer that progressed during or after anti-endocrine therapy (Turner et al. 2015). The palbociclib/Faslodex combination was found to be well tolerated. Additionally, there is growing data indicating that this combination can be safely and effectively administered up front in anti-endocrine therapy-naive patients in the neoadjuvant setting.

Gedatolisib (code name PF-05212384, formerly known as PKI-587) is an intravenous (IV) adenosine triphosphate (ATP) competitive, highly selective and potent inhibitor of pan-class I isoform phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3-K) and mammalian target of rapamycin (mTOR) (Fry et al. 2004). Preclinical and first-in-human studies have shown a manageable safety profile with predictable toxicity for this class of drugs.

Activation of the PI3-K/*Akt*/mTOR/p-S6 pathway has been associated with endocrine resistance in ER+ breast cancer. There is ample evidence that inhibition of this pathway, in combination with anti-hormonal therapy, increases PFS (Baselga et al. 2012). There is also clinical evidence that combination therapy targeting all three pathways is feasible, safe and effective (Sweeney et al. 2014). The advantage of Gedatolisib is its potential to inhibit signaling through different PI3-K isoforms. Also important is the fact that once a week administration may be as effective, but less toxic, than chronic oral dosing. If hyperglycemia is a surrogate for effective PI3-K/*Akt*/mTOR/p-S6 inhibition, once weekly dosing of Gedatolisib would appear to accomplish equivalent degrees of hyperglycemia as chronically oral dosing and with less toxicity.

Preoperative or neoadjuvant systemic chemotherapy, once reserved for patients with locally advanced breast cancer in whom the goal was to render large breast cancers operable, has become increasingly common due to the improvement in disease-free survival and overall survival. Historically, the endpoint of pathological Complete Response (pCR) in neoadjuvant therapy against ER+/HER2- breast cancer has been of limited value. However, new targeted agents, with higher response rates, have the potential to use pCR assessment as a strong clinical endpoint in drug development. Given the systemic response rate in previously treated Stage IV breast cancer patients, the expectation will be a similar high rate of pathological improvement which can lead to greater use of targeted agents in the neoadjuvant setting.

In addition to the potential of better pathological improvement, the advantage of clinical studies involving neoadjuvant therapy is that they can provide response information in patients that are treatment-naïve. This type of clinical trial can also be used to assess cellular and molecular changes with serial biopsies while on neoadjuvant therapy, which can aid in

development of companion tissue and/or imaging biomarkers, and further the development of preclinical models.

Accordingly, this investigation assesses the safety and efficacy of the combination of Gedatolisib, palbociclib and faslodex in the neoadjuvant setting in previously untreated patients with ER+/HER2- breast cancer. Being the first clinical trial using this combination in neoadjuvant setting, one of the main objectives for the current trial is to determine the Maximum Tolerated Dose (MTD) of Gedatolisib when used in combination with palbociclib and faslodex. Subsequent Phase II clinical trials will be conducted to assess the safety and efficacy of the Gedatolisib/palbociclib/faslodex combination, with the dose of Gedatolisib being the MTD determined from the current trial.

1.2 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, 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.

2. STUDY DRUG - Gedatolisib

2.1 Formulation, Pharmaceutical Properties and Administration

Gedatolisib drug product is lyophilized powder (or cake) in a glass vial. This formulation contains 50 mg/mL Gedatolisib and precedented excipients, with appropriate packaging.

Gedatolisib drug product is to be reconstituted using an appropriate volume of sterile Water for Injection. After reconstitution, the solution is added to an appropriate volume of 5% Dextrose for Injection prior to administration as an IV infusion.

Under ambient light and room temperature conditions, the reconstituted solution can be stored for up to four hours and the prepared dosing solution for up to 24 hours.

As with all parenteral products, the preparation and administration of Gedatolisib drug product in the clinic should be conducted with appropriate aseptic technique and the infusion commenced as soon as practical, but no longer than four hours after drug product reconstitution or 24 hours after dilution with 5% dextrose injection.

Gedatolisib drug product is incompatible with sodium chloride and chloride ion-containing medication. The use of saline and other chloride containing medication should be avoided during preparation and administration of Gedatolisib drug product.

Gedatolisib drug product, at escalating doses of 180, 215 and 260 mg, is to be administered as an IV infusion over 30 minutes once weekly in 28-day cycles for a total of four cycles.

2.2 Request for Gedatolisib Drug Product

Complete the Drug Supply Request Form provided by Pfizer, Inc. The Drug Supply Request Form lists the required information and contact information for requesting Gedatolisib drug product.

The Principal Investigator should maintain a drug inventory sufficient to treat study subjects for approximately four (4) weeks while waiting for additional ordered supplies.

Gedatolisib may not be used outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in this clinical study.

2.3 Procurement of Investigational Drug

Relevant regulations require investigators to establish a record of the receipt, use and disposition of all investigational products. Investigators may delegate responsibility of drug ordering, storage, accountability and preparation to the designees.

The investigator, or the designee, will be responsible for dispensing and accounting of Gedatolisib drug product and for exercising accepted medical and pharmacy practices.

Records of inventory, dispensation and disposition (vials received, source and dates) must be maintained. In addition, all doses dispensed should be accounted for by recording the date, study number and name, patient identification, patient initials, patient medical record number and balance forward. These records must be maintained and kept at the study site.

2.4 Disposal of Gedatolisib Drug Product

The following procedures are to be taken in disposal of Gedatolisib drug product:

- During the study, store the used Gedatolisib vials (which must be separate from the unused Gedatolisib vials) at room temperature in an access-limited area. Alternatively, destroy the used Gedatolisib vials according to institutional policy after documentation of the number of used Gedatolisib vials and remaining volume in each used vial.
- At the end of the study, deface the label (both used and unused vials) with a permanent marking pen.
- For used Gedatolisib vials (if not already destroyed according to institutional policy), after documentation of the number of used Gedatolisib units and remaining volume in each container, the used containers should be destroyed at the site according to the institutional procedures for destroying toxic chemicals. A certificate documenting the destruction of used vials must be kept on file.
- All unused Gedatolisib vials must be destroyed according to the policy of the institution. The destruction of Gedatolisib, and the quantity destroyed, must be documented.

3. STUDY SUBJECTS AND PROTECTION

3.1 Eligibility Criteria, Concomitant and Prophylactic Treatment, Registration and Enrollment, Identification of Study Subjects

3.1.1 Eligibility 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.)
   - the disease is previously untreated for breast cancer, operable and intended 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 the 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 1:** In patients with Stage III disease, PET/CT imaging studies are 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 procedure:
   - Obtaining the required research 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 [AST/SGOT] ≤3x upper normal limit [UNL], alanine aminotransferase [ALT/SGPT] ≤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)

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.

3.1.2 Concomitant Medications and Prophylactic Treatment

Patients cannot receive any standard or investigational treatment (except those related to this study) for their cancer, or any other investigational drugs for any indications, while on this study. All concomitant medications (including trade and generic names, dosage and dosing schedule) must be recorded.

Prophylactic treatment for Gedatolisib-related symptoms is not planned, or it will interfere with the assessment of the toxicity of the investigational product. However, following the evaluation of the causal relationship of the symptom(s) to the study drug and the information has been documented, the investigator may prescribe supportive treatment. Supportive treatment may include anti-emetic, anti-diarrhea, anti-pyretic, anti-allergic, anti-hypertensive medications, analgesics, antibiotics, allopurinol, granulocyte colony stimulating factor (G-CSF) and others such as blood products at the discretion of the treating physicians. Also, the hemoglobin should be maintained ≥9 g/dL or ≥90 g/L during the course of the study.

Since oral mucositis was observed in ~50% of patients treated with the PF-05212384/ cisplatln combination, the general guidelines as concomitant treatments in the prophylaxis and management of oral mucositis are outlined below:

Oral Mucositis - General Guidelines for Prophylaxis, Concomitant Treatments, and Management

- Patients who have not had a dental checkup within 6 mos prior to start of dosing are encouraged to do so.
- Patient should perform a steroid containing "swish-and-spit" regimen (e.g., dexamethasone 0.5 mg/5 mL swish and expectorate, four times daily.)
  - Pre-dose on Cycle 1 Day 1 as prevention and use on a continued basis as clinically indicated.
  - The daily number of steroid containing mouth rinses can be reduced as clinically indicated.

- Topical anesthetics or systemic analgesics may be used as indicated according to the judgment of the investigator and according to local clinical practices.
- Use of chlorhexidine is to be avoided.

Additionally, skin rashes have been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, FOLFIRI, PD-0325901, docetaxel, cisplatin, or dacomitinib. Benadryl can be given approx. 30 minutes prior to infusion of Gedatolisib.

3.1.3 Registration, Pre-Enrollment Medical Screening and Enrollment of Study Subjects

Patients Registration

At the time of registration, the eligibility checklist is reviewed, verified and signed. If the eligibility requirements are satisfied, the patient can be considered for pre-enrollment medical screening (see next section).

Pre-Enrollment Medical Screening

Informed consent must be obtained prior to pre-enrollment medical screening. Investigators who are listed on US "FDA Form 1572" (or investigator's designee) are authorized to obtain informed consent. Pre-enrollment medical screening is used to determine the eligibility of each candidate, and it is to be performed within two weeks prior to neoadjuvant treatment, except that radiographic tumor response assessments can be performed within 4 weeks.

Subject Enrollment

Patients meeting all criteria stated in Section 3.1.1 are eligible for admission to the study.

3.1.4 Identification of Study Subjects

In addition to the study number, each study site will be assigned a site number or code. Furthermore, at the inception of the study, study subjects will be sequentially assigned numbers (e.g., 001, 002, 003, etc.) in the order of study entry at their respective site. Therefore, the subject will be identified by "study number - study site/code - study subject number".

3.2 Protection of Human Subjects

3.2.1 Institutional Review Board (IRB)

Before implementing this study, the protocol, informed consent and any amendments must be reviewed and approved by an IRB. A copy of the IRB approval letter must be provided to Dr. Anthony Hoffman or the designee. Until such written approval from the IRB has been received by the investigator and a copy provided to Dr. Anthony Hoffman or the designee,

and until the proper submission of appropriate documents to the regulatory agencies and other regulatory requirements have been met, no patient should undergo any procedures for the purpose of determining eligibility for this study.

3.2.2 Informed Consent

Patients will be required to sign a statement of informed consent, which meets Good Clinical Practices (GCP) and local regulatory requirements (e.g., U.S. 21 Code of Federal Regulations [CFR] 50). The medical record will include a statement indicating that written informed consent has been obtained, and the date informed consent is obtained, before enrollment in the study. Members of the treating team (such as those listed in the FDA Form 1572 or Canadian "Clinical Trial Site Information Form" if applicable), or investigator's designee (such as the study nurse), will review to the patients the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, and alternative therapies (including best supportive care). Patients must be informed that participation in the study is voluntary, he/she may withdraw from the study at any time, and withdrawal from the study will not affect his/her subsequent medical treatment or relationship with the treating physician. Financial costs that will or may be incurred as a result of participation in the study, as well as the efforts to maintain patient confidentiality will also be discussed. The informed consent will be signed by the patient and registering physician (or investigator's designee such as the study nurse). A signed copy will be given to the patient. The original will be placed in the medical record at the study site.

3.2.3 Protection of Privacy

The investigator agrees to maintain in confidence all data generated in the study, except as provided or required by law, and will divulge such information to the IRB with the understanding that confidentially will be maintained.

4. STUDY DESIGN AND PROCEDURES

4.1 Study Objectives

The primary objectives of the current study are to determine:

- Safety, tolerability and potential efficacy of Gedatolisib when used in combination with palbociclib and Faslodex, 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 the neoadjuvant setting 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.

4.2 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 intend to undergo surgery after four cycles of therapy.

This is an open-label study, and investigators and subjects are not blinded to the treatment. The reason for using an open-label study design is 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.

4.3 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 4.3-1 (below).

Table 4.3-1: 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 or intramuscularly; IV; intravenous or intravenously; PO = oral or orally; SC = subcutaneous or subcutaneously.

* 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.

Specifically, the four drugs are administered as outlined below:

- Gedatolisib at escalating doses of 180, 215 and 260 mg via a 3-6 dose-escalation scheme is administered once weekly on the first day for each of the four weeks during the four 4-week cycles.
- Faslodex at 500 mg is administered IM into the buttocks slowly (over 1 - 2 minutes per injection) as two 5-mL injections, one in each buttock, on Days 1 and 15 of Cycle 1 and on Day 1 of the remaining three 4-week treatment cycles.
- Palbociclib at 125 mg is administered PO with food daily on Days 1-21 for each of the four 4-week cycles.
- Zoladex, Eligard or Lupron is used to render menopause in pre-menopausal subjects, given once every 28 days or monthly starting 1 week prior to treatment.

4.4 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. (i.e., Level -1). If DLT is also observed in two or more patients at 150 mg (i.e., Level -1), 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 will be 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.

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 an 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.

4.5 Justification of the Starting Dose in the Dose Escalation Scheme

The current study investigates, among other objectives, safety and tolerability of weekly IV escalating doses of Gedatolisib at 180 mg, 215 mg and 260 mg, when used in combination with Palbociclib and Faslodex, in previously untreated patients with ER+/HER2- breast cancer prior to tumor excisional surgery. Patients will receive four 4-week cycles of the neoadjuvant therapy.

The starting dose of 180 mg is expected to be safe, based on interim results from ongoing clinical trials, as described below.

A Phase 1 single agent trial has been conducted with weekly IV administration of Gedatolisib in dose-escalation manner in patients with solid tumor (Study B2151001, ClinicalTrials.gov Identifier NCT00940498). This study did not include doses between 154 and 222 mg. Therefore, the MTD of Gedatolisib is in this dose range.

A Phase 1b dose-escalation trial, in which weekly IV administration of Gedatolisib in dose-escalation manner is used in combination with various different anti-tumor agents in patients with solid tumor, is ongoing (Study# B2151002, ClinicalTrials.gov Identifier NCT01920061). Interim results show that, when used in combination with 75 mg/m^2 cisplatin, Gedatolisib at doses of 154 mg, 180 mg, 215 mg and 260 mg is free of DLT and well tolerated. The safety and tolerability of 315 mg of Gedatolisib is currently being tested. Therefore, the MTD of Gedatolisib when used in combination with these drugs is above 260 mg.

When used in combination with 75 mg/m^2 docetaxel, Gedatolisib at doses up to 180 mg is free of DLT in a recent clinical trial. Doses higher than 180 mg were not tested due to termination of the trial because of a change in priority.

Since safety and tolerability of Gedatolisib is established at doses as high as 215 mg when used in combination with 75 mg/m^2 cisplatin, and as high as 180 mg when used in combination with 75 mg/m^2 docetaxel, Gedatolisib at the starting dose of 180 mg is expected to be safe.

4.6 Dosing Delay and Dose Modification in the Event of Adverse Events

4.6.1 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 4.6.1-1 (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 4.6.1-1: 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.

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:
  - Withhold dose of Gedatolisib and Palbociclib until toxicity is Grade ≤ 2, then resume treatment at *next lower dose of each agent*.
  - 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:
  - Withhold dose of Gedatolisib and Palbociclib until toxicity is Grade ≤2, then resume treatment at *next lower dose of each agent*.
  - 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.
- 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:
  - Initiate clinically appropriate monitoring.
  - Reduce at *next lower dose of each agent*.
  - 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 the initiation of the next cycle by a maximum of 2 weeks.

* At discontinuation of therapy, operable patients should proceed promptly to surgery.

4.6.2 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.

4.7 Withdrawal from Study

Patients are withdrawn from the study if:

- Patients exhibit progression of disease based on radiologic and/or symptoms assessment
- Unacceptable toxicity from Gedatolisib
- Patient withdrawal of consent
- Investigator's discretion to withdraw patients from the study because continued participation in the study is not in the patient's best interest.
- Inter-current illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible
- General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment

- Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits
- Termination of the clinical trial by the sponsor

When terminating treatment during this trial, the investigator should make every effort to contact the patient and to perform a final evaluation. Also, the reason(s) for withdrawal from the study must be recorded.

4.8 Study Procedures

Table 4.8-1 (next page) provides an overview of the study procedures. The specifics are described in subsequent sections.

4.8.1 Screening

The following procedures will be performed during patient screening, and the screening procedures must be performed within two weeks prior to neoadjuvant chemotherapy, except that radiographic tumor response assessments can be performed within 4 weeks. The specifics of these tests are described in Section 4.9.

- medical history and current medications
- cancer history (date of diagnosis, current stage of disease, date of diagnosis of the current stage of disease, and cancer-related treatment history)
- Hemoglobin A1c
- ECG, assessed at baseline to exclude subjects with a marked prolongation of QT/QTc interval (e.g., repeated exhibition of a QTc interval >470 ms)
- physical exam, body weight and height
- vital signs and evaluation of symptoms
- pregnancy test for women of child-bearing potential (obtain within 2 weeks prior to treatment initiation) (pregnancy test is also performed at least monthly in pre-menopausal women.)
- safety assessments:
  - fasting serum glucose, fasting triglycerides, insulin, C-peptide and cholesterol. 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)
  - blood work (clinical chemistry, hematology and coagulation)
- tumor response assessments:
  - radiographic tumor response assessments
  - clinical tumor response assessments (physical exam of the breast and axilla)
- efficacy and biomarkers/genomics:
  - tumor tissues obtained via needle biopsy for pCR background information and genomics via the Foundation CDx™ test. Extra tumor samples, if available, are stored for possible future testing.

- whole blood samples 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.

4.8.2 Safety and Efficacy Assessments During and After the Study

The following safety and efficacy assessments will be performed during and after the study:

- physical exam, body weight, vital signs and evaluation of symptoms will be performed immediately before Gedatolisib administration. They can be performed whenever clinically indicated.
- vital signs and evaluation of symptoms will be performed immediately after Gedatolisib administration. They can be performed whenever clinically indicated.
- blood work (clinical chemistry, hematology and coagulation), as well as 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. Insulin, C-peptide and cholesterol, as well as hemoglobin A1c are performed at baseline and before surgery.
- efficacy and biomarkers/genomics:
  - Tumor tissues are obtained post-treatment from tumor excision surgery to assess pCR and genomics via the Foundation CDx™ test. Extra tumor samples, if available, are stored for possible future testing
  - Whole blood samples are obtained 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

Table 4.8-1: 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 [1]
		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]	√																													
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.

[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 was 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 clinical 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.

4.9 Specifics of Tests Performed During the Study

4.9.1 Safety

Fasting Serum Glucose, Fasting Triglycerides, Insulin, C-Peptide and Cholesterol

Fasting serum glucose will be assessed in the clinic at baseline and on Day 1 of each of the four treatment cycles during neoadjuvant therapy. Fasting triglycerides will be assessed in the clinic at baseline. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment). Insulin, C-peptide and cholesterol will be assessed in the clinic at baseline and before surgery. For the first day of the first week of Cycle 1, the results from screening can be used.

Clinical Chemistry

Clinical chemistry will be assessed at baseline, weekly on the first day of each week of the four 4-week treatment cycles, and before surgery. During neoadjuvant therapy, clinical chemistry is to be performed with results available for review within 72 hours prior to the start of treatment each week. For the first day of the first week of Cycle 1, the results from screening can be used. Clinical chemistry includes:

creatinine	PO_4
total protein	uric acid
albumin	blood urea nitrogen (BUN)
Na^+	AST/serum glutamic-oxaloacetic transaminase (SGOT)
K^+	ALT/serum glutamic-pyruvic transaminase (SGPT)
Cl^-	alkaline phosphatase (ALP)
Mg	lactate dehydrogenase (LDH)
Ca^{+2}	total bilirubin

Hematology

Hematology will be assessed at baseline, weekly on the first day of each week of the four 4-week treatment cycles, and before surgery. During neoadjuvant therapy, hematology is to be performed with results available for review within 72 hours prior to the start of treatment each week. For the first day of the first week of Cycle 1, the results from screening can be used. Hematology includes:

complete blood count	hemoglobin
differential count	hematocrit
platelet count	

Coagulation will be assessed at baseline, weekly on the first day of each week of the four 4-week treatment cycles, and before surgery. During neoadjuvant therapy, coagulation is to be performed with results available for review within 72 hours prior to the start of treatment each week. For the first day of the first week of Cycle 1, the results from screening can be

used. Coagulation includes:

INR	Partial thromboplastin time

4.9.2 Tumor Response Assessments

Radiographic Tumor Response Assessments

Radiographic tumor response assessments are performed at baseline (within 4 weeks prior to neoadjuvant therapy), 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.

Clinical Tumor Response Assessments

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.

4.9.3 Efficacy and Biomarkers/Genomics

Pathological Complete Response (pCR) (and pCR Background Information at Baseline)

Tumor tissues will be obtained to assess pCR background information at baseline and pCR post-treatment from tumor excision surgery. The definition of pCR is the absence of residual invasive and *in situ* cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypN0 in the current American Joint Committee on Cancer [AJCC] staging system). The definition of pCR background information is hematoxylin and eosin evaluation of the breast specimen obtained via needle biopsy obtained at baseline.

pCR rate will be used as an indication of treatment response to the investigational neoadjuvant therapy. The endpoint of pCR in neoadjuvant therapy in breast cancer has been shown to correlate with drug effectiveness and OS advantage. The FDA accepts pCR as a clinical endpoint for drug development and product approval (FDA Guidance for Industry 2014).

Foundation CDx™ Test on Tumor Tissues

Genomics of tumor tissues are assessed using the Foundation CDx test. Detailed information of this test can be obtained from the FoundationOne website: https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx. Briefly,

FoundationOne CDx is the first FDA-approved broad companion diagnostic (CDx) test that is clinically and analytically validated for solid tumors. The test is designed to provide physicians with clinically actionable information - both to consider appropriate therapies for patients and understand results with evidence of resistance - based on the individual genomic profile of each patient's cancer. Every test result includes microsatellite instability (MSI) and tumor mutational burden (TMB) to help inform immunotherapy decisions.

The sampling and shipment procedures are provided in Appendix A. Contact information for ordering the sample kits is also included. Investigators should order the sample kits at least 3-5 days in advance to allow sufficient time for delivery of the sample kits from FoundationOne to the study site.

FoundationOne®Liquid Test on Whole Blood

In all 3 parts of the study, genomic test on liquid biopsy for solid tumors that analyze circulating tumor DNA in blood are assessed via the FoundationOne®Liquid test.

The sampling and shipment procedures are provided in Appendix B. Contact information for ordering the sample kits is also included. Investigators should order the sample kits at least 3-5 days in advance to allow sufficient time for delivery of the sample kits from FoundationOne to the study site.

4.10 Surgery for Breast Cancer After Neoadjuvant Therapy

Tumor excision surgery will be performed three weeks after the four treatment cycles of neoadjuvant therapy, or until vital signs, symptoms and clinical lab values return to normal. Surgery can be performed with total WBC >3,000 cells/mm^3 or 3.5 bil/L. 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.

Patients should receive the standard of care following neoadjuvant chemotherapy and surgery, including hormonal therapy for a minimum of five years, chemotherapy and radiation therapy if indicated.

When surgery is performed three weeks after the four treatment cycles, the time between the last doses of various drugs and surgery would be as listed below:

- seven weeks minus one day after the last dose of Faslodex
- four weeks after the last dose of Palbociclib
- four weeks minus one day after the last dose of Gedatolisib

The type of tumor excision surgical procedures (e.g., lumpectomy or breast conserving surgery; partial or segmental mastectomy or quadrantectomy; simple or total mastectomy; radical mastectomy; modified radical mastectomy, etc.) considered to be the most appropriate for the study subjects will be determined by the surgeon. Any complication, and the nature of complication, during surgery should be documented for potential correlation with neoadjuvant

therapy.

4.11 Statistical Analysis

This is a dose-escalation Phase Ib study with the primary objectives of assessing the safety, tolerability and MTD of Gedatolisib when used in combination with palbociclib and Faslodex in the neoadjuvant setting in previously untreated patients with ER+/HER2- breast cancer. The secondary objective is to assess pCR induced by the combination of Gedatolisib, palbociclib and Faslodex in these patients. Exploratory objectives include assessments of 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.

Due to the small sample size of 3-6 patients per cohort with expansion of the MTD cohort to a total of 18 patients in this trial in this dose-escalation trial, outcome from any statistical analysis will not be reliable. As such, the analyses of the results from this trial will be primarily descriptive.

Safety and toxicities for the 18 patients in this trial will be assessed by examining each adverse event by grade.

For the assessment of pCR, the portion of patients who achieve pCR will be presented. Presentation of pCR rate data will include mean and 95% confidence intervals.

For the assessments of genomic results from Foundation CDx™ on tumor tissues and FoundationOne®Liquid on peripheral whole blood, potential correlation of treatment response to these parameters will be evaluated.

5. GUIDELINES FOR INVESTIGATORS

Guideline information related to Gedatolisib for investigators is summarized below. Detailed information can be obtained from the Investigator's Brochure.

5.1 Contraindications

There are no specific contraindications for Gedatolisib.

5.2 Special Warnings and Precautions for Use

5.2.1 Mucosal Inflammation and Stomatitis

Mucosal inflammation and stomatitis have been reported in patients treated with Gedatolisib alone, and when used in combination with irinotecan, PD-0325901 (a MAPK/ERK kinase [MEK] inhibitor), docetaxel, cisplatin, or dacomitinib.

Investigators should employ prophylactic measures and treatment options to reduce the incidence and severity of oral complications. Severe oral toxicities can compromise the delivery of an adequate dose intensity of the planned cancer treatment, due to dose reduction or treatment schedule modifications necessary to allow for resolution of oral lesions. Reduced dose intensities may potentially reduce the antitumor efficacy of the anticancer treatment.

Management of oral complications of Gedatolisib includes identification of high-risk populations, patient education, initiation of pretreatment interventions, and timely management of lesions.

Assessment of oral status before treatment with Gedatolisib is critical to overall patient care. Care should be both preventive and therapeutic to minimize risk for oral and associated systemic complications.

Specific recommendations for minimizing oral mucosal inflammation (stomatitis) include the following:

- Good oral hygiene (i.e., thorough and frequent cleaning of the oral cavity)
- Avoidance of spicy, acidic, hard, and hot foods and beverages
- Use of mild-flavored toothpastes
- Use of saline-peroxide mouthwashes 3 or 4 times per day

Specific recommendations for managing mucositis include the following:

- Bland rinses:
  - 0.9% saline solution;
  - Sodium bicarbonate solution;
  - 0.9% saline/sodium bicarbonate solution.
- Topical anesthetics:

- Lidocaine: viscous, ointments, sprays
- Benzocaine: sprays, gels
- 0.5% or 1.0% dyclonine hydrochloride
- Diphenhydramine solution

• Mucosal coating agents:
- Aluminum hydroxide
- Bismuth Subsalicylate
- Hydroxypropyl methycellulose film-forming agents
- Polyvinylpyrrolidone-sodium hyaluronate gel

• Analgesics:
- Benzydamine HCI topical rinse
- Opioid drugs: oral, intravenous (e.g., bolus, continuous infusion, patient controlled analgesia [PCA], patches, transmucosal
- Anti-inflammatory treatment as required

(Nonsteroidal anti-inflammatory drugs that affect platelet adhesion and damage gastric mucosa are contraindicated, especially if thrombocytopenia is present.)

• Aggressive antimicrobial treatment for any new mouth infections.

For additional recommendations regarding the prevention and treatment of mucositis, refer to the American Society of Clinical Oncology (ASCO) guidelines (Keefe et al 2007).

5.2.2 Drug-Induced Pneumonitis

Drug-induced pneumonitis was not reported in clinical trials in which Gedatolisib is used alone. One patient treated with Gedatolisib in combination with dacomitinib experienced Grade 3 drug-induced pneumonitis. The investigator considered the event to be related to dacomitinib and not Gedatolisib. No other Gedatolisib-treated patients experienced drug-induced pneumonitis.

Drugs which are mTOR inhibitors are known to be associated with pulmonary toxicity. Drug-induced pneumonitis was reported observed in patients treated with temsirolimus (Duran et. al. 2006). Approximately 50% of patients were symptomatic, and dyspnea and dry cough were the most frequently observed symptoms. Two different radiological patterns were described, including ground glass opacities and lung parenchymal consolidation. The management of this toxicity was variable, ranging from no intervention, corticosteroid treatment to discontinuation of the drug. The presentation and its severity are also variable.

Monitoring for drug-induced pneumonitis, and other respiratory events, is recommended. The risk of developing this toxicity may be increased among subjects with abnormal pretreatment pulmonary functions or history of lung disease.

5.2.3 Nausea and Vomiting

Nausea and vomiting have been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, PD-0325901, docetaxel, cisplatin, or dacomitinib.

The routine prophylactic use of antiemetic medications is not recommended up to the first observation of Grade ≥2 nausea and/or vomiting. Once the patient's sensitivity to the emetogenic activity of Gedatolisib or Gedatolisib -based regimen is identified, the most appropriate antiemetic prophylaxis should be adopted. The drug regimen for antiemetic prophylaxis and treatment should be selected according to the Investigator's clinical judgment and experience.

5.2.4 Diarrhea

Diarrhea has been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, FOLFIRI, PD-0325901, docetaxel, cisplatin, or dacomitinib.

Anti-diarrheal measures should be started at the earliest sign of any of the following:

- Poorly formed or loose stool
- Occurrence of 1 or 2 more bowel movements than usual in 1 day
- Significant increase in stool volume or decreased fecal consistency

Patients should be instructed to refer immediately to the site in case of these symptoms. The regimen for anti-diarrheal treatment will be at the discretion of the Investigator.

5.2.5 Asthenia and Fatigue

Asthenia and/or fatigue have been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, FOLFIRI, PD-0325901, docetaxel, cisplatin, or dacomitinib.

Fatigue is common in patients with cancer and the correction of potential co-morbidities (e.g., anemia, electrolyte imbalances, and depression) may be a useful approach to limit the severity of the event. Approaches to the diagnosis and the management of cancer-related fatigue are discussed in the National Comprehensive Cancer Network Guideline for Cancer Related Fatigue.

5.2.6 Hyperglycemia

Hyperglycemia, as a laboratory abnormality, has been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, FOLFIRI, PD-0325901, docetaxel, cisplatin, or dacomitinib.

The PI3-K/mTOR pathway is known to be important in the maintenance of glucose homeostasis. The inhibition of PI3-K/mTOR is frequently associated with hyperglycemia and is a known class effect. Patients treated with Gedatolisib should be monitored for glucose blood levels.

The following guidelines (see Table 5.2.6-1, below) are general strategies that investigators may consider implementing in patients with hyperglycemia; these guidelines are not mandatory and are not meant to replace institutional practices.

On-study hyperglycemia management:

- If FBG ≥200 mg/dL, repeat FBG in 1 week.

Table 5.2.6-1: Guidelines for Hyperglycemia Management

FBG	Management[¥]
≥160 mg/dL, on 2 readings 1 week apart	• Patients without history of DM o Lifestyle modification o Initiate metformin therapy* o If FBG ≥200 mg/dL, initiate home monitoring QD. o If FBG >200-250 mg/dL after 2 weeks of metformin: ▪ Continue metformin and add sulfonylurea [¥],** o If FBG ≥250 mg/dL after 1 week ▪ Add sulfonylurea** or ▪ Add insulin and titrate to maintain FBG <200 mg/dL Targets of treatment - Fasting / AC (before meal) glucose: <160 mg/dL - Random glucose: <200 mg/dL - Avoid hypoglycemia • Patients with history of DM o Titrate current medications to maintain FBG <200 mg/dL o Consult with endocrinologist/primary care physician who is following DM
Symptomatic[§] Grade 3 (250-500 mg/dL)	• IV fluids and consider hospitalization • Consider holding PI3-K inhibitor dose until ≤Grade 2 or baseline and then restarting at original dose level
Grade 4	• IV fluids and consider hospitalization • Consider holding PI3-K inhibitor dose until ≤Grade 2 or baseline and then restarting at 1 lower dose level
Grade 4 despite optimal anti-hyperglycemic therapy	• IV fluids and consider hospitalization • Discontinue treatment

AC = ante clbum (before meals); DM = Diabetes Mellitus; FBG = fasting blood glucose; IV = intravenous or intravenously; QD = once daily

* Contraindicated in patients with renal insufficiency

[¥] Discontinue oral hypoglycemic agents and monitor for hypoglycemia when PF-05212384 is interrupted for lengthy periods or is discontinued

** Can also use meglitinide-class drugs, especially short acting agents (e.g., repaglinide)

[§] Symptoms such as, but not limited to hypotension, severe dehydration, severe metabolic abnormalities manifested as ECG changes

5.2.7 Decreased Appetite

Decreased appetite has been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, PD-0325901, cisplatin, or dacomitinib.

Similar to fatigue, decreased appetite is a multi-factorial condition in patients with cancer. Treatment of potentially reversible complications such as infection, uncontrolled pain, or depression may be useful to mitigate the severity of decreased appetite.

5.2.8 Skin Effects

Skin effects have been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, FOLFIRI, PD-0325901, docetaxel, cisplatin, or dacomitinib. The reported skin effects include: dry skin, acneiform dermatitis, palmar-plantar erythrodysaesthesia syndrome, pruritus, rash (generalized rash, rash erythematous, rash maculopapular, rash macular, rash papular, skin exfoliation, and catheter site rash), skin infection, skin lesion, skin fissures, skin inflammation, eczema, erythema, catheter site erythema, and cellulitis.

Patients should be informed about the frequent related cutaneous adverse reactions associated with Gedatolisib and the need to avoid exposure to extreme temperatures, the use of lotions (since lotions can contain alcohol) and direct sunlight (or tanning beds). The use of preventive topical treatments, such as bathing techniques using bath oils or mild moisturizing soaps and bathing in tepid water may help to prevent the appearance of cutaneous toxicity or reduce its intensity. The use of regular moisturizing creams is also recommended to keep an appropriate skin hydration and humidity, which is useful to reduce the symptoms in case of rash appearance.

5.2.9 Hematological Abnormalities

Hematological abnormalities have been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, PD-0325901, docetaxel, cisplatin, or dacomitinib. Examples of hematological abnormalities include: anemia, lymphopenia, white blood cell decrease, neutrophil count decrease

Anemia, although of multifactorial etiology in patients with advanced cancer, is probably related to the role of the PI3-K/mTOR pathway in the expansion of erythroid progenitors (Bakker et. al., 2004) and inhibition of this pathway by PF-05212384. Lymphopenia is likely secondary to the inhibition of the PI3-K isoforms gamma and delta, which play an essential role in lymphocyte development and differentiation (Ghigo et. al., 20 10).

As of 29 May 2014, no clinical implications, e.g., opportunistic infections, for treatment related lymphopenia have been observed. Therefore there are no specific recommendations for management of lymphopenia. However, considering the role of the PI3-K/mTOR pathway in the bone marrow physiology, Gedatolisib should be administered with caution to patients with abnormal blood counts and complete blood counts (CBC) should be monitored following treatment with Gedatolisib.

5.2.10 Elevation of Liver Enzymes

Elevation of liver enzymes (ALT, AST, bilirubin, and/or alkaline phosphatase), as laboratory abnormalities, have been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, PD-0325901, docetaxel, cisplatin, or dacomitinib.

In most cases, the transaminase values returned to baseline value after treatment interruption. The elevated alkaline phosphatase and bilirubin were not reported as AEs and likely related to progression of the underlying malignancy.

Only patients with non-clinically significant alterations of liver function should receive Gedatolisib. Additionally, patients being treated with Gedatolisib should be routinely monitored for elevation of liver enzymes.

5.2.11 Use in Patients with Renal Impairment

Elevations of creatinine, as laboratory abnormalities, have been reported in patients treated with Gedatolisib alone, and when Gedatolisib is used in combination with irinotecan, PD-0325901, docetaxel, cisplatin, or dacomitinib.

The mild renal toxicity associated with PF-05212384 may be related to the physiological role of the PI3-K/mTOR pathway in the tubular and glomerular cell physiology.

Only patients with non-clinically significant alterations of kidney function should receive Gedatolisib. Careful attention should be paid to concomitant clinical situations which may impair renal function (e.g., dehydration) as well as concomitant nephrotoxic medications.

5.3 Interaction with Other Medicinal Products and other Forms of Interaction

No clinical information is currently available regarding the potential for drug-drug interactions with Gedatolisib and co-administrated drugs.

5.4 Fertility, Pregnancy, and Lactation

Gedatolisib was assessed in a series of genetic toxicology assays consisting of the microbial reverse mutation, *in vitro* cytogenetic (human lymphocyte), and *in vivo* rat micronucleus assays. All *in vitro* tests were conducted with and without exogenous metabolic activation using concentrations up to those limited by cytotoxicity or insolubility.

Gedatolisib was not genotoxic in either *in vitro* or *in vivo* assays. Gedatolisib has not been tested for carcinogenic activity in a lifetime rodent bioassay.

Safety for women of child-bearing capacity cannot be implied from the existing data. Women of child-bearing potential (not surgically sterile or postmenopausal) must use effective contraception while receiving trial treatment and for three months thereafter. Women of child-

bearing potential should also have a negative pregnancy test prior to treatment with Gedatolisib.

No studies have been conducted in humans to assess the impact of Gedatolisib on milk production, its presence in breast milk and its effects on the breast-fed child. Since drugs are commonly excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, lactating female patients should not be treated with Gedatolisib.

5.5 Effects on Ability to Drive and Use Machines

Patients should be instructed to avoid potentially hazardous tasks such as driving or operating machinery if they experience dizziness following treatment with Gedatolisib.

5.6 Reference Safety Information

Table 5.6-1 (below) represents the adverse drug reaction observed among patients receiving single Gedatolisib.

Table 5.6-1: Summary of Adverse Drug Reactions Following IV Administration of Single Gedatolisib [a]

System Organ Class	ADR (by Preferred Term)	Frequency (%)
Gastrointestinal Disorders	Nausea	54.9
	Mucosal Inflammation	54.9
	Vomiting	35.4
	Diarrhea	32.9
	Stomatitis	15.9
	Dry Mouth	13.4
General Disorders and Administration Site Conditions	Asthenia	28.0
	Pyrexia	19.5
	Fatigue	30.5
Hepatobiliary Disorders	Aspartate aminotransferase increased	13.4
	Alanine aminotransferase increased	12.2
Metabolism and Nutrition Disorders	Appetite decreased	40.2
	Hyperglycemia	23.2
	Dehydration	6.1
Nervous System Disorders	Dysgeusia	26.8
Skin and Subcutaneous Tissue Disorders	Rash	18.3
	Dry skin	7.3
	Pruritus	9.8
	Dermatitis acneiform	3.7

IV = intravenous
[a] Dose of Gedatolisib was 154 mg, given once weekly.

5.7 Overdose

No information regarding overdose of Gedatolisib in humans is available. In the event of an accidental overdose, the subject should be monitored for the possible signs of toxicity as mentioned above. In addition, Dr. Anthony Hoffman (or designee) should be notified. As

there is no specific antidote for overdose of Gedatolisib, general supportive care should be provided.

5.8 Drug Abuse and Dependence

No data are available regarding long term administration and the potential dependence on Gedatolisib.

6. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

6.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered with an investigational product and does not necessarily have to have a causal relationship with the investigational product. An AE can therefore be any unfavorable and unintended sign (including an abnormal lab finding), symptom or disease temporally associated with the use of the investigational product. This includes worsening of a pre-existing condition or increase in frequency of a pre-existing condition. An AE is considered serious if it meets the serious criteria described in Section 6.3 (below). To avoid confusion or misunderstanding of the difference between "serious" and "severe", which are not synonymous, the following clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose that a causal relationship between the medicinal product and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out). An unexpected ADR is any adverse reaction not consistent with the specificity and severity as that described in the latest Investigator's Brochure or the clinical protocol.

6.2 Adverse Event Grading, Recording and Reporting

The physician or designee is to question the patient about AEs and intercurrent illnesses since the last assessment and is to record the information in the subjects' medical record. The questioning of subjects regarding AE is generalized such as, "How have you been feeling since your last visit?" The onset and end dates, severity, and relationship to study drug are to be recorded for each AE. The severity of the AE is to be assessed and graded according the NCI CTC.

Any lab value considered by the investigator to be clinically significant should be considered an AE. However, abnormal clinical lab values of clinical significance which were present at baseline and did not change in severity or frequency during the investigational treatment or can obviously be attributed to the underlying disease will not be considered an ADR. Significant abnormal values occurring during the trial will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

If a patient becomes pregnant while on the study, the investigational treatment will be immediately stopped. The investigator is required to report the pregnancy to Dr. Anthony Hoffman or the designee, within 24 hours via telephone or fax. If initially reported via telephone, it must be followed-up with a written report via fax within 24 hours of the telephone

report. Pregnancy must be followed to term and outcome of the pregnancy must also be reported.

All AEs will be evaluated by the investigator for potential relationship to the investigational treatment in the following categories:

Unrelated:	The AE is clearly not related to the investigational drug.
Unlikely	The AE is unlikely related to the investigational drug.
Possibly Related	The AE is possibly related to the investigational drug.
Likely:	The AE may be related to the investigational drug.
Definitely:	The AE is clearly related to the investigational drug.

Patients who experience AEs will be monitored with clinical assessments and lab tests, as determined appropriate by the investigator. All AEs are to be followed to satisfactory resolution or stabilization of the event(s). Any action taken or outcome (e.g., hospitalization, discontinuation of therapy, etc.) as well as follow-up tests are to be recorded in the patient's medical record. Follow-up test and/or lab results are to be filed with the patient's source documentation.

All AEs are documented, kept as part of the patient's medical record and recorded using AE Case Report Form (to be provided to the investigators). All AEs are reported in the annual progress reports to Dr. Anthony Hoffman/designee, the IRB, FDA (via Dr. Anthony Hoffman/designee), and Pfizer, Inc. (via Dr. Anthony Hoffman/designee).

6.3 Serious Adverse Events

A serious adverse event (SAE) is defined as an untoward (unfavorable) medical occurrence that at any dose:

- Results in death,
- Is life-threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Results in a congenital anomaly /birth defect, or
- Jeopardizes the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Important medical events that do not result in death, are not life-threatening, or do not require hospitalization can be considered SAEs when, based upon appropriate medical judgment, they jeopardize the subject or require medical or surgical intervention to prevent any of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions not requiring hospitalization; or development of drug dependency or drug abuse.

6.4 Serious Adverse Event Recording and Reporting

Any SAE, including death from any cause that occurs starting from the first dose of the investigational drug to within 30 days after stopping the study drug (regardless of relationship to study drug), must be recorded using the SAE Report Form (to be provided by Dr. Anthony Hoffman or the designee) and reported to the Medical Monitor (see front page of this protocol) and Dr. Anthony Hoffman/designee immediately via telephone or fax within 24 hours. If initially reported via telephone, this must be followed-up with a written report via fax within 24 hours of the telephone report. It is important to mark on the SAE Report Form the potential relationship to the investigational treatment in the following categories:

Unrelated:	The SAE is clearly not related to the investigational drug.
Unlikely	The SAE is unlikely related to the investigational drug.
Possibly Related	The SAE is possibly related to the investigational drug.
Likely:	The SAE may be related to the investigational drug.
Definitely:	The SAE is clearly related to the investigational drug.

Where relationship to the investigational product is uncertain or unknown (such as in the event of a blinded study, if applicable), the SAE must still be recorded using the SAE Report Form but should be marked "unknown" relationship with investigational drug. Expected SAE (i.e., those described in the Investigator's Brochure) do not require expedited, but still needs to be captured as SAE using the SAE Report Form. AEs that are classified as unexpected and serious, but are unrelated to the investigational drugs will not be reported by expedited means.

Any SAE occurring at any other time after completion of the study must also be recorded using the SAE Report Form and must be promptly reported to IRB, Dr. Anthony Hoffman/designee, FDA (via Dr. Anthony Hoffman/designee), and Pfizer, Inc. (via Dr. Anthony Hoffman/designee), if a causal relationship to the study drug is suspected. If initially reported via telephone, this must be followed-up with a written report via fax within 24 hours of the telephone report.

The investigator (or the designee) is required to fill out the SAE Report Form. Sufficient details must be provided to allow for a medical assessment of the SAE and independent determination of possible causality. The investigator is obliged to pursue and provide additional information as requested by Dr. Anthony Hoffman, or the designee. Follow-up information about a previously reported SAE must be reported within 72 hours of receipt.

Dr. Anthony Hoffman (the sponsor) is required to report to the regulatory agencies, other study sites involved in clinical trials of Gedatolisib, and Pfizer, Inc. (the sponsor of Gedatolisib), in an expedited manner, all unexpected SAEs that are associated with the use of the investigational product. Therefore, it is imperative that Dr. Anthony Hoffman (or the designee) be informed within 24 hours of any SAE (including overdose) as noted above, so that reporting to the regulatory agencies can be met within the required time frame. It is the responsibility of the investigator to promptly notify the IRB of all AEs, SAEs and/or ADRs according to institutional guidelines and applicable local laws and regulations.

7. COMPLIANCE, PROTOCOL AMENDMENT, AND DATA MANAGEMENT

7.1 Compliance

This study will be conducted according to GCP, applicable regulatory requirements and applicable institutional guidelines. The investigator will conduct the study in compliance with the protocol and approved by the IRB unless the modification is needed to eliminate an immediate hazard to patients. In this case, the IRB and FDA (via Dr. Anthony Hoffman/designee) must be promptly notified.

Investigators are required to ensure compliance with respect to the investigational drug schedule, visit schedule and procedures stated in the protocol. Appropriate written justification must be documented by the investigator for all inadvertent departures from protocol requirements.

7.2 Protocol Amendments

Changes to a protocol must be implemented by a formal protocol amendment. Amendments to the protocol must be initiated by the sponsor of the trial. The formal amendment must be signed by the principal investigator, approved by the IRB, and submitted to the regulatory agencies, prior to implementation. If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the patient's rights, full IRB approval must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the patient's rights, IRB approval may be obtained by expedited review. A modification to the protocol may be initiated without IRB approval or without prior submission to the regulatory agencies ONLY when the change is necessary to eliminate apparent immediate hazard to the patients. In that event, the investigator must notify, in writing, Dr. Anthony Hoffman/designee, the IRB, FDA (via Dr. Anthony Hoffman/designee), and Pfizer (Dr. Anthony Hoffman/designee).

In some cases, an amendment may require a change to a consent form. The investigator must receive IRB approval prior to implementing the revising informed consent. Additionally, changes to the case report forms (CRFs), if required, will be incorporated in the amendment.

7.3 CRFs

Dr. Anthony Hoffman (or designee) will provide the study site with CRFs for each patient. The investigator or designee should complete the CRFs expeditiously to capture all the relevant information. The investigator (or his/her designee) must also follow the instructions for providing signature and date, as well as in handling missing data, incorrect data entry, etc.

7.4 Data Entry

A Research Study Assistant (RSA) will be assigned by the principal investigator to the study at the study site. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and

prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secured database designed and maintained by Dr. Anthony Hoffman or its designee. Source documentation must be available to support the computerized patient record.

7.5 Record Maintenance

All study records will be retained for at least 2 years after the last marketing approval, or 2 years after discontinuation of the clinical development of the investigational drug. In the event that the FDA, Health Canada, EMEA or other regulatory agencies contact the investigator for the purposes of an audit of the study, the investigator will notify Dr. Anthony Hoffman immediately.

If the investigator relocates to another institution, the responsibility of keeping the study records must be transferred to another person at the current institution and Dr. Anthony Hoffman must be notified in writing if such a change should occur.

8. PATIENT AND STUDY DISCONTINUATION

Listed below are criteria for the discontinuation of the study. However, patients who fail to return for the follow-up visits will be contacted and queried as to the reason they have failed to complete the study with special attention to health status.

A. Patients have the right to withdraw from the study at any time for any reason.

B. The investigator has the right to withdraw patients from the study according to his/her discretion, if the investigator determines that continued participation is not in the patient's best interest. As an excessive rate of withdrawals can render the study not interpretable, unnecessary withdrawal of patients should be avoided. When a patient discontinues investigational treatment, the investigator should make every effort to contact the patient and to perform a final evaluation. The reason(s) for withdrawal must be recorded. Criteria for terminating subject's participation in the study are listed below:

- Disease progression significantly greater than expected
- Unacceptable toxicity of the investigational product
- Patient withdrawal of consent
- Investigator's discretion
- Intercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible
- General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment
- Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits
- Termination of the clinical trial by the sponsor (see below)

C. Dr. Anthony Hoffman (sponsor) has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- Patient enrollment is unsatisfactory
- Quality or quantity of data recording is inaccurate or incomplete
- The incidence or severity of ADRs in this or other studies indicates a potential health hazard to patients
- Poor adherence to protocol and regulatory requirements
- Plans to modify or discontinue the development of the investigational product

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APPENDICES

Appendix D: Sampling and Shipment Procedures for FoundationOne CDx

Specimen Instructions

FOUNDATIONONE CDx™

FoundationOne CDx™ is a broad companion diagnostic (CDx) test for five tumor indications. In addition to use as a companion diagnostic, F1CDx provides cancer relevant alterations that may inform patient management in accordance with professional guidelines. Information generated by this test is an aid in the identification of patients who are most likely to benefit from associated therapeutic products as noted in Table 1 of the Intended Use.[1]

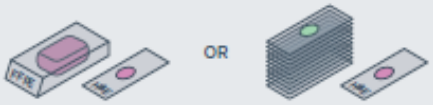
Acceptable Samples

- Formalin-fixed paraffin embedded (FFPE) specimens, including cut slide specimens are acceptable.
- Use standard fixation methods to preserve nucleic acid integrity. 10% neutral-buffered formalin for 6–72 hours is industry standard. DO NOT use other fixatives (Bouins, B5, AZF, Holland's).
- Do not decalcify.

☐ **SAMPLE SIZE**

1 When feasible, please send the block + 1 H&E slide.*

10 unstained slides (positively charged and unbaked at 4-5 microns thick) + 1 H&E slide.*

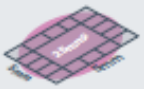


For smaller samples, providing the original H&E will preserve material for testing.

☐ **SURFACE AREA**

2 **MINIMUM: 25 mm²**

If sending slides, provide 10 unstained slides cut at 4-5 microns thick to achieve a tissue volume of 1 mm³.**



**Specimens with a smaller surface area may meet volume requirements by submitting additional unstained slides (USS) or block.*

☐ **TUMOR CONTENT**

3 **OPTIMUM: 30% TN MINIMUM: 20% TN**

Percent tumor nuclei (%TN) = number of tumor cells divided by total number of all cells with nuclei

Note for liver specimens: higher tumor content may be required because hepatocyte nuclei have twice the DNA content of other somatic nuclei

Shipping Instructions

1. Place the samples, FoundationOne CDx™ requisition form, insurance information, and any other attachments into the FoundationOne CDx Specimen Shipping Kit.
2. Place the specimen shipping kit (including samples and paperwork) into the provided FedEx shipping pack, first ensuring that primary specimen containers (e.g. blocks, slides) are labeled with two patient-specific identifiers. Seal the shipping pack.
3. Complete the pre-printed shipping labels (if necessary) and apply to shipping pack.
4. Call 800.463.3339 to request a pick-up or drop the package at your site's designated FedEx pick-up location and ship sealed shipping pack to:

Foundation Medicine, Inc.
150 Second Street
Cambridge, MA 02141
Phone: 888.988.3639

FOUNDATION MEDICINE®

www.foundationmedicine.com | Tel. 888.988.3639 | Fax 617.418.2290 | MKT-0082-02

Intended Use

FoundationOne CDx™ (F1CDx) is a next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

Table 1: Companion diagnostic indications

INDICATIONS	BIOMARKER	FDA-APPROVED THERAPY*
Non-Small Cell Lung Cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E or V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib), in combination with Zelboraf® (vemurafenib)
Breast Cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
Colorectal Cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3 and 4) and *NRAS* wild-type (absence of mutations in exons 2, 3 and 4)	Vectibix® (panitumumab)
Ovarian Cancer	*BRCA1/2* alterations	Rubraca® (rucaparib)

Reference

1. For full information on the intended use, assay descriptions, and for detailed performance specifications, refer to the complete FoundationOne CDx label at www.foundationmedicine.com/f1cdx.

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Appendix B: Sampling and Shipment Procedures for FoundationOne®Liquid

Specimen Instructions

FOUNDATIONONE®LIQUID

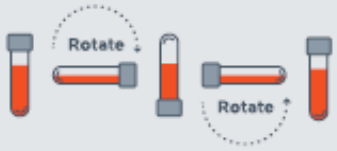
Peripheral Whole Blood

Use only tubes provided inside the FoundationOne®Liquid Specimen Collection and Shipping Kit.
Other tubes will not be accepted.

Instructions For Use

Accurate analysis of cell-free DNA requires proper collection technique and handling of the sample. Failure to adhere to these instructions can compromise results by diluting cell-free DNA with DNA from white blood cell lysis.

- ☐ 1 Check special tubes provided in FoundationOne Liquid kits to confirm liquid is clear and without cloudiness or crystals.
- ☐ 2 Label tubes with date of collection and two patient identifiers.
- ☐ 3 Collect two tubes of whole blood (8.5mL per tube).
  - Prevent backflow: tubes contain chemical additives and it is important to avoid backflow into patient.
  - Collect specimen by venipuncture according to CLSI H3-A6.[1]
  - Fill tubes completely (8.5mL per tube).
- ☐ 4 Remove the tube from adapter and immediately **mix by gentle inversion 8 to 10 times.** Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180°, and back per the figure below.



- ☐ 5 Place specimen, completed requisition form (TRF) (remember to include patient's diagnosis), insurance information, available reports, and accompanying documents into the FoundationOne Liquid Specimen Collection and Shipping Kit (copies of pathology reports and/or other clinical documentation).
  - Confirm each tube is labeled with the supplied labels indicating the date of collection and two unique patient identifiers (label included in kit).
- ☐ 6 Preferably on the same day of collection, ship via FedEx priority overnight delivery at ambient temperature. Do not freeze or refrigerate blood samples.

  Temperature is important. Keep at room temperature (43-99° F, 6-37° C).

  DO NOT FREEZE.

Shipping Instructions

1. Place the samples, FoundationOne Liquid requisition form, insurance information, and any other attachments into the FoundationOne Liquid Specimen Collection and Shipping Kit.
2. Place the specimen kit (including samples and paperwork) into the provided FedEx shipping pack, first ensuring that primary specimen containers (e.g. tubes) are labeled with two patient-specific identifiers. Seal the shipping pack.
3. Complete the pre-printed shipping labels (if necessary) and apply to shipping pack.
4. Call 800.463.3339 to request a pick-up or drop the package at your site's designated FedEx pick-up location and ship sealed shipping pack to:

Foundation Medicine, Inc.
150 Second Street
Cambridge, MA 02141
Phone: 888.988.3639

Reference
1. Clinical and Laboratory Standards Institute. H3-A6, Procedures for the collection of diagnostic blood specimens by venipuncture; approved standard-sixth edition.

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