Official Title: An Open-Label, Phase Ia/Ib/IIa Study of GDC-0810 Single Agent or in Combination With Palbociclib and/or an LHRH Agonist in Women With Locally Advanced or Metastatic Estrogen Receptor Positive Breast Cancer

NCT Number: NCT01823835

Document Date: Protocol Version 9: 25-January-2017

PROTOCOL

TITLE:	**AN OPEN-LABEL, PHASE Ia/Ib/IIa STUDY OF GDC-0810 SINGLE AGENT OR IN COMBINATION WITH PALBOCICLIB AND/OR AN LHRH AGONIST IN WOMEN WITH LOCALLY ADVANCED OR METASTATIC ESTROGEN RECEPTOR POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	GO29642
VERSION NUMBER:	*9*
EUDRACT NUMBER:	2014-004852-77
IND NUMBER:	116019
TEST PRODUCT:	GDC-0810 (RO7056118)
MEDICAL MONITOR:	[redacted] M.D., Ph.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 17 December 2012
DATES AMENDED:	Version 2: 24 January 2013–Amendment 1 Version 3: 8 February 2013–Amendment 2 Version 4: 23 April 2013–Amendment 3 Version 5: 11 October 2013–Amendment 4 Version 6: 20 June 2014–Amendment 5 Version 7: 2 January 2015–Amendment 6 Version 8: *18 December 2015–Amendment 7* *Version 9:* See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	25-Jan-2017 04:31:48

PROTOCOL AMENDMENT, VERSION 9:
RATIONALE

Protocol GO29642 has been amended to reduce the number of required study procedures as a result of Sponsor decision to halt the development of GDC-0810 and halt enrollment into the study. The decision to halt the development of GDC-0810 is not due to any safety concerns. Adverse events observed for GDC-0810 alone or in combination with luteinizing hormone-releasing hormone (LHRH) agonist or palbociclib thus far are similar to those that have been observed with other endocrine agents and are amenable to monitoring, are manageable, and reversible.

As a result of the decision to halt development of GDC-0810, the following changes have been made:

- Enrollment in this study has been discontinued. Therefore, no further patients will be enrolled.
- Patients experiencing clinical benefit may continue to receive GDC-0810 as a single agent or in combination with LHRH agonist or palbociclib until progression of disease, unacceptable toxicity, consent withdrawal, GDC-0810 drug supply has been exhausted, or the Sponsor terminates the study.
- Limited Physical exam, ECOG, vital signs, liver function tests, creatinine, adverse events, concomitant medication, study drug compliance will be collected at least monthly and as clinically indicated.
- Hematology (for patients receiving GDC-0810 alone or in combination with LHRH agonist), blood chemistry (except creatinine and liver function tests), urinalysis, bone scans, and CT/MRI scans will be collected per institutional guidelines and as clinically indicated.
- Hematology will be collected at least monthly and as clinically indicated for patients receiving GDC-0810 in combination with palbociclib.
- The frequency of transvaginal ultrasounds has been changed from every 6 months to as clinically indicated due to the low rate of adverse events observed and to align with the other ongoing GDC-0810 study (GO29689). Collection of the transvaginal ultrasound at the end of treatment will continue.
- No new or potential safety risks have been identified; however, on the basis of accumulated clinical experience, dose modification guidelines have been updated.
- Collection of fasting lipid panel has been removed because it is not essential for ongoing safety monitoring.
- Clinical and nonclinical summaries have been update to align with the GDC-0810 Investigator's Brochure, Version 4.
- The definition of the end of study has been revised because of the Sponsor's decision to halt the development of GDC-0810.
- Post-trial access to GDC-0810 has been revised because of the Sponsor's decision to halt the development of GDC-0810.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, PHASE Ia/Ib/IIa STUDY OF GDC-0810 SINGLE AGENT OR IN COMBINATION WITH PALBOCICLIB AND/OR AN LHRH AGONIST IN WOMEN WITH LOCALLY ADVANCED OR METASTATIC ESTROGEN RECEPTOR POSITIVE BREAST CANCER**
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MEDICAL MONITOR:	[redacted] M.D., Ph.D.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form and forward a copy to:

[redacted]
PPD Inc.
9330 Scranton Road, Suite #200
San Diego Ca 92121
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, PHASE Ia/Ib/IIa STUDY OF GDC-0810 SINGLE AGENT OR IN COMBINATION WITH PALBOCICLIB AND/OR AN LHRH AGONIST IN WOMEN WITH LOCALLY ADVANCED OR METASTATIC ESTROGEN RECEPTOR POSITIVE BREAST CANCER**
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PHASE:	Phase Ia/Ib/IIa
INDICATION:	Breast cancer
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

Primary Objective

Phase Ia

- To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D)and assess the safety of single agent GDC-0810 in postmenopausal women with locally advanced or metastatic estrogen-receptor-positive (ER+) and human epidermal-growth-factor-negative (HER2−) breast cancer

Phase IIa

- To determine the anti-tumor activity of single agent GDC-0810 in postmenopausal women with locally advanced or metastatic ER+ (HER2−) breast cancer

Phase Ib

- To determine the RP2D and assess the safety and tolerability of concomitant administration of GDC-0810 with palbociclib and/or luteinizing hormone-releasing hormone (LHRH) agonist in women with locally advanced or metastatic ER+ (HER2−) breast cancer

Secondary Objectives

Phase Ia

- To evaluate the pharmacokinetics of GDC-0810 single agent and its glucuronide metabolites following single and multiple dose treatments.

Phase IIa

- To evaluate the safety of GDC-0810 single agent when administered at the RP2Ds in women with locally advanced or metastatic ER+ (HER2−) breast cancer
- To evaluate the effect of GDC-0810 single agent on ventricular repolarization in postmenopausal women participating in the Phase IIa portion of the study

Phase Ib

- To evaluate the pharmacokinetics of GDC-0810 in combination with palbociclib and/or an LHRH agonist.

- To evaluate the pharmacokinetics of palbociclib and/or an LHRH agonist in combination with GDC-0810

Exploratory Objectives

- To perform exploratory evaluation of biomarkers of PD response with [^{18}F]-fluoroestradiol (FES)- positron emitting tomography (PET) in Phase Ia and Phase IIa
- To perform exploratory evaluation of ER target gene expression
- To perform exploratory evaluation of mechanisms of resistance to GDC-0810

Study Design

Description of Study

This is a multi-institution Phase Ia/Ib/IIa open-label, dose-finding, safety, PK, and proof-of-concept study of GDC-0810 as a single agent and in combination with palbociclib and/or LHRH agonist.

The study is divided into three phases: Phase Ia, Phase Ib, and Phase IIa. The Phase Ib palbociclib combination cohorts will be conducted in the U.S. only and the LHRH agonists combination cohorts will be conducted in the U.S. and South Korea. The Phase Ia and IIa part of the study (single agent GDC-0810 cohorts) will be conducted in Spain, Netherlands South Korea and the U.S.

Enrollment in Study GO29642 has been discontinued; therefore, no patients will be enrolled in the Phase Ib Cohorts C2, C3, and D2. Any patient currently enrolled in Phase Ia, Ib Cohort C1, Ib Cohort D1, or IIa experiencing clinical benefit may continue to receive GDC-0810 as a single agent or combination with LHRH agonist or palbociclib until disease progression, unmanageable toxicity, patient withdrawal of consent, GDC-0810 drug supply has been exhausted, or the Sponsor terminates the study.

Phase Ia

Phase Ia consists of dose escalation in postmenopausal women with locally advanced or metastatic ER+ (HER2−) breast cancer *and enrollment into dose escalation cohorts has been completed*.

During Phase Ia, GDC-0810 single agent *was* administered orally to postmenopausal women with locally advanced or metastatic ER+ (HER2−) breast cancer on a continuous daily dosing regimen with a Day −7 lead-in period for single dose PK evaluation prior to the start of daily treatment. The incidence of DLTs will be evaluated from Day −7 through the first cycle (28 days) of treatment (35 days total). Depending on safety and tolerability, patients will be assigned sequentially to escalating doses of GDC-0810 using standard 3 + 3 design.

The starting dose will be 100 mg once daily. Dosing will be based on flat milligram increments without adjustments for body size. It is anticipated that dose levels will span the anticipated pharmacologically active dose range and be within the safety margin indicated by nonclinical toxicology studies. The dosing regimen may be changed if the PK and safety data suggest that a discontinuous regimen or another dosing frequency (e.g., twice daily [BID]), with or without a fasting requirement, may be preferable for the Phase IIa portion of the study.

Phase IIa

Expansion cohorts consisting of a total of 100 postmenopausal women with locally advanced or metastatic ER+ (HER2−) breast cancer previously treated with an aromatase inhibitor (AI) will be treated at the RP2D to further characterize the safety, PK, PD, and anti-tumor activity of GDC-0810 as follows:

- **Cohort A:** 30 patients who have confirmed ER-α (ESR1) mutation of the ligand-binding domain (LBD), further divided into 2 subsets:

  Cohort A1: 20 patients who had **no** prior treatment with fulvestrant. FES-PET will be obtained for PD analysis only in Cohort A1.

  Cohort A2: 10 patients where prior treatment with fulvestrant is allowed
- **Cohort B:** 70 patients who have progressed following ≤ 1 prior therapy with an AI in the advanced/metastatic setting, further divided into 2 subsets:

  Cohort B1: 50 patients who had **no** prior treatment with fulvestrant

  Cohort B2: 20 patients where prior treatment with fulvestrant is allowed

During the Phase Ib and Phase IIa portion of the study, there will be no PK week lead-in period (i.e., all eligible patients will start continuous daily dosing treatment on Cycle 1 Day 1).

The effect of GDC-0810 on ventricular repolarization will be evaluated in all patients enrolled in the Phase IIa portion of the study.

After enrollment is complete in Cohorts A2, B1, and B2 of the Phase IIa portion of the study, further enrollment in Cohort A1 may be discontinued. *Enrollment in the Phase IIa portion of the study is complete.*

All patients will be treated until disease progression, unacceptable toxicity, or patient withdrawal of consent.

Phase Ib

Enrollment in Study GO29642 has been discontinued; therefore, no patients will be enrolled in the Phase Ib Cohorts C2, C3, and D2.

In Cohorts C1, C2, and C3 of the Phase Ib study (dose escalation and expansion), GDC-0810 will be administered orally on Days 1–28 of a 28-day schedule and 125 mg palbociclib will be administered on Days 1–21 of a 28-day schedule to women with locally advanced or metastatic ER+ (HER2–) breast cancer. In Cohorts C1 and C2 (dose escalation), patients will be assigned sequentially to escalating doses of GDC-0810 using standard 3 + 3 design. If the MTD is exceeded at dose level C1 (or the dose level is deemed intolerable in the absence of dose limiting toxicities), de-escalation to dose level C0 may occur. Palbociclib dose de-escalation below 75 mg/day is not allowed, but the schedule may be changed in consultation with the Medical Monitor for example to 75 mg/day 2 weeks on followed by 2 weeks off (2/2 schedule). The starting dose of GDC-0810 will be 400 mg daily, one dose level below the single agent RP2D.

In Cohort C3, up to 6 pre- or perimenopausal women may be enrolled to receive a combination of GDC-0810 (28/0), LHRH every 4 weeks (Q4W), and palbociclib (21/7).

In Phase Ib Cohort D1 (safety run-in cohort) and Cohort D2 (dose expansion), GDC-0810 will be administered orally on Days 1–28 of a 28-day schedule and an LHRH agonist administered monthly. The GDC-810 dose for Cohort D1 will be 600 mg daily. There will be no dose escalation of either study drug or study drug treatment. *No* patients will be enrolled in Cohort D2.

For Cohorts, C1, C2 and D1, the incidence of DLTs will be evaluated from Days 1 to 28 of Cycle 1.

Number of Patients

- Phase I: 21 to 42, depending on how many doses are needed to reach the MTD and/or RP2D
- Phase IIa: 100 Target Population
- Phase Ib: Approximately *5* patients *have been* enrolled in the Phase Ib dose escalation cohorts (Cohorts C0 *and* C1). *No additional patients will be enrolled.*

  Approximately *4* patients *have been* enrolled at the RP2D of GDC-0810 and palbociclib, and approximately *6* patients *have been* enrolled at 600 mg of GDC-0810 and an LHRH agonist

Target Population

Phase Ia Inclusion Criteria

Patients must meet the following criteria for study entry:

- Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either locally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease, both progressing after at least 6 months of endocrine therapy for ER+ breast cancer
- ER-positive tumor (staining in ≥ 1% cells by immunohistochemistry [IHC] as per local laboratory testing)
- HER2-negative breast cancer as per local laboratory testing (IHC result of 0 or +1 for cellular membrane protein expression or a fluorescence in situ hybridization [FISH] result showing HER2/CEP17 ratio < 1.8 or an average of fewer than 4 copies of *HER2* gene per nucleus for systems without an internal control probe)
- At least 2 months must have elapsed from the use of tamoxifen
- At least 6 months must have elapsed from the use of fulvestrant
- At least 2 weeks must have elapsed from the use of any other anti-cancer hormonal therapy
- At least 3 weeks must have elapsed from the use of any chemotherapy
- Females, 18 years of age or older
- Postmenopausal status defined as:

  Prior bilateral surgical oophorectomy

  Age ≥ 56 years: natural amenorrhea with ≥ 1 year since last menses

  Age < 56 years with amenorrhea ≥ 1 year since last menses and serum estradiol levels (< 20 pg/mL) and follicle-stimulating hormone (FSH) levels (> 40 mIU/mL) in the postmenopausal range

  Age < 56 years who had hysterectomy with one or both ovaries left in place, or with tamoxifen-induced amenorrhea together with a tamoxifen discontinuation of ≥ 1 year and serum estradiol levels (< 20 pg/mL) and FSH levels (> 40 mIU/mL) in the postmenopausal range

  Age < 56 years who have medical menopause on LHRH agonist (on stable dose ≥ 1 year) with amenorrhea ≥ 1 year since last menses and serum estradiol levels in the postmenopausal range (< 20 pg/mL) irrespective of FSH/LH levels for Phase Ia; medical menopause is defined as ovarian suppression by any medical cause including treatment with LHRH agonist, radiation, or surgery causing inhibition of pituitary gonadotropin secretion, irrespective of FSH/LH levels.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Resolution of all acute toxic effects of prior therapy or surgical procedures to baseline or Grade ≤ 1 (except alopecia or other toxicities not considered to be a safety risk for the patient)
- Adequate organ function as defined by the following criteria:

  Absolute neutrophil count (ANC) ≥ 1500/μL

  Platelets ≥ 100,000/μL

  Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 3 times the upper limit of normal (ULN) or AST and ALT ≤ 5 × ULN if liver function abnormalities are due to underlying malignancy or liver metastasis

  Total serum bilirubin ≤ 1.5 × ULN regardless of liver involvement secondary to tumor. Inclusion of patients with increased serum indirect bilirubin (≤ 3 × ULN) due to Gilbert's syndrome is permitted.

  Serum creatinine ≤ 1.5 × ULN

  QTc ≤ 460 msec
- Signed and dated informed consent document indicating that the subject has been informed of all the pertinent aspects of the trial prior to enrollment

- Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures
- For women of childbearing potential (including patients with menopause induced by LHRH agonists): agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of LHRH agonist or 28 days after the last dose of GDC-0810 and palbociclib (whichever is latest)

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Phase Ia Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Untreated or symptomatic CNS metastases.

  Note: Patients with treated and asymptomatic CNS metastases that are radiographically stable within 12 weeks prior to enrollment will be allowed, provided long-term use of corticosteroids has been discontinued within 4 weeks prior to enrollment.
- Patients with a history of endometrial polyps, endometrial cancer, atypical endometrial hyperplasia, or other significant endometrial disorders should be excluded unless they have undergone total hysterectomy and there is no evidence of active disease.
- More than two prior chemotherapies in the advanced/metastatic setting (prior adjuvant chemotherapy is allowed so long as it occurred ≥ 12 months prior to enrollment)
- Current treatment with any systemic anti-cancer therapies for advanced disease or any systemic experimental treatment on another clinical trial
- Diagnosis of any secondary malignancy within 2 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ
- Any of the following within 12 months prior to enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of Grade ≥ 2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, or cerebrovascular accident including transient ischemic attack
- Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or upper gastrointestinal surgery including gastric resection
- Known human immunodeficiency virus (HIV) infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., hepatitis B or hepatitis C virus), current alcohol abuse, or cirrhosis
- Major surgery within 4 weeks prior to enrollment
- Radiation therapy within 2 weeks prior to enrollment
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study

Phase IIa Inclusion Criteria

- Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either locally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease, both progressing after at least 6 months of endocrine therapy with an aromatase inhibitor for ER+ breast cancer
- ER-positive tumor (staining in ≥ 1% cells by IHC as per local laboratory testing)
- HER2-negative breast cancer as per local laboratory testing (IHC result of 0 or +1 for cellular membrane protein expression or a FISH result showing HER2/CEP17 ratio < 1.8 or an average of fewer than 4 copies of *HER2* gene per nucleus for systems without an internal control probe)
- Cohort A only:

  Confirmed ESR1 mutations of the LBD (as determined in a Clinical Laboratory Improvement Amendments [CLIA]-certified laboratory) and consent to provide an archival tumor sample for retrospective confirmation (LBD further defined as the region between ER-α amino acids 302 to 595) and

  Presence of evaluable disease as per RECIST Version 1 further defined as follows:

  Measurable disease, or evaluable bone disease—that is, bone lesions that are lytic or mixed (lytic + sclerotic) in the absence of measurable lesion. Note: previously irradiated lesions are deemed measurable only if progression is documented at the site after completion of radiation.
- For patients with soft tissue or visceral metastases that are safely accessible, paired pre- and on-treatment tumor biopsies are required.

  Cohort A1 only: No prior fulvestrant allowed; at least 2 months must have elapsed from the use of tamoxifen (if applicable)

  Cohort A2 only: Prior fulvestrant allowed

- **Cohort B only:** Disease progression following ≤ 1 prior treatment with an AI in the advanced/metastatic setting (prior adjuvant treatment with an AI is allowed):

  Patients must have relapsed ≥ 12 months from completion of adjuvant treatment **or** progressed following ≥ 6 months of treatment in the advanced/metastatic setting.

  Measurable disease, or evaluable bone disease—that is, bone lesions that are lytic or mixed (lytic + sclerotic) in the absence of measurable lesion. Note: previously irradiated lesions are deemed measurable only if progression is documented at the site after completion of radiation.

  Cohort B1 only: No prior fulvestrant allowed

  Cohort B2 only: Prior fulvestrant allowed

- At least 2 weeks must have elapsed from the use of the most recent endocrine therapy (for Cohort A1, if most recent endocrine therapy is tamoxifen, see inclusion criterion above)
- At least 3 weeks must have elapsed from the use of any chemotherapy
- Females, 18 years of age or older
- Postmenopausal status defined as:

  Prior bilateral surgical oophorectomy

  Age ≥ 56 years: natural amenorrhea with ≥ 1 year since last menses

  Age < 56 years with amenorrhea ≥ 1 year since last menses and serum estradiol levels (< 20 pg/mL) and FSH levels (> 40 mIU/mL) in the postmenopausal range

  Age < 56 years who had hysterectomy with one or both ovaries left in place, or with tamoxifen-induced amenorrhea together with a tamoxifen discontinuation of ≥ 1 year and serum estradiol levels (< 20 pg/mL) and FSH levels (> 40 mIU/mL) in the postmenopausal range

Age < 56 years who have medical menopause, such as LHRH agonist (on stable dose ≥ 1 year) with amenorrhea ≥ 1 year since last menses and serum estradiol levels in the postmenopausal range (< 20 pg/mL) irrespective of FSH/LH levels. Cause of medical menopause should be discussed with the Medical Monitor.

- ECOG performance status 0 or 1
- Resolution of all acute toxic effects of prior therapy or surgical procedures to baseline or Grade ≤ 1 (except alopecia or other toxicities not considered to be a safety risk for the patient)
- Adequate organ function as defined by the following criteria:

  Absolute neutrophil count (ANC) ≥ 1500/ L

  Platelets ≥ 100,000/ L

  Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 3 × ULN, or AST and ALT ≤ 5 × ULN if liver function abnormalities are due to underlying malignancy or liver metastasis

  Total serum bilirubin ≤ 1.5 × ULN regardless of liver involvement secondary to tumor. Inclusion of patients with increased serum indirect bilirubin (≤ 3 × ULN) due to Gilbert's syndrome is permitted

  Serum creatinine ≤ 1.5 × ULN

  QTc ≤ 460 msec
- Signed and dated informed consent document indicating that the subject has been informed of all the pertinent aspects of the trial prior to enrollment
- Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures
- For women of childbearing potential (including patients with menopause induced by LHRH agonists): agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of LHRH agonist or 28 days after the last dose of GDC-0810 and palbociclib (whichever is latest).

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Phase IIa Exclusion Criteria

- Untreated or symptomatic CNS metastases.

  Note: Patients with treated and asymptomatic CNS metastases that are radiographically stable within 12 weeks prior to enrollment will be allowed, provided long-term use of corticosteroids have been discontinued within 4 weeks prior to enrollment
- Patients with a history of endometrial polyps, endometrial cancer, atypical endometrial hyperplasia, or other significant endometrial disorders should be excluded unless they have undergone total hysterectomy and there is no evidence of active disease.

- Prior treatments:

EXCLUSIONS	Prior Endocrine Therapy	Prior Chemotherapy
Cohort A1	▪ Fulvestrant	▪ > 1 prior chemotherapy in the advanced/metastatic setting
Cohort A2		▪ > 1 prior chemotherapy in the advanced/metastatic setting
Cohort B1	▪ > 1 prior AI in the advanced/metastatic setting ▪ Fulvestrant	▪ Prior chemotherapy in the advanced/metastatic setting (prior adjuvant chemotherapy is allowed so long as it occurred ≥ 12 months prior to enrollment)
Cohort B2	▪ > 1 prior AI in the advanced/metastatic setting	▪ > 1 prior chemotherapy in the advanced/metastatic setting

- Current treatment with any systemic anti-cancer therapies for advanced disease
- Diagnosis of any secondary malignancy within 2 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ
- Any of the following within 12 months prior to enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of Grade ≥ 2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, or cerebrovascular accident including transient ischemic attack
- Active inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), any active bowel inflammation (including diverticulitis), chronic diarrhea, short bowel syndrome, or history of upper gastrointestinal surgery including gastric resection
- Known human immunodeficiency virus infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., Hepatitis B or Hepatitis C virus), current alcohol abuse, or cirrhosis
- Major surgery within 4 weeks prior to enrollment
- Radiation therapy within 2 weeks prior to enrollment
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study

Phase Ib Inclusion Criteria

- Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either locally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease
- Documented sensitivity to prior hormonal therapy (Relapsed after 24 mo of adjuvant endocrine therapy or had a clinical benefit from prior endocrine therapy in the context of advanced disease)

- ER-positive tumor (staining in ≥ 1% cells by immunohistochemistry [IHC] as per local laboratory testing)
- HER2-negative breast cancer as per local laboratory testing (IHC result of 0 or +1 for cellular membrane protein expression or a FISH result showing HER2/CEP17 ratio < 1.8 or an average of fewer than 4 copies of HER2 gene per nucleus for systems without an internal control probe)
- At least 2 weeks must have elapsed from the use of any other anti-cancer hormonal therapy excluding LHRH agonist for patients enrolled in Cohorts C3, D1 and D2
- At least 3 weeks must have elapsed from the use of any chemotherapy
- Females, 18 years of age or older
- Postmenopausal status defined as:

  Prior bilateral surgical oophorectomy

  Age ≥ 56 years: natural amenorrhea with ≥ 1 year since last menses

  Age < 56 years with amenorrhea ≥ 1 year since last menses and serum estradiol levels (< 20 pg/mL) and follicle stimulating hormone (FSH) levels (> 40 mIU/mL) in the postmenopausal range

  Age < 56 years who had hysterectomy with one or both ovaries left in place, or with tamoxifen-induced amenorrhea together with a tamoxifen discontinuation of ≥ 1 year and serum estradiol levels (< 20 pg/mL) and FSH levels (> 40 mIU/mL) in the postmenopausal range

  Age < 56 years who have medical menopause on LHRH agonist (on stable dose ≥ 1 year) with amenorrhea ≥ 1 year since last menses and serum estradiol levels in the postmenopausal range (< 20 pg/mL) irrespective of FSH/LH levels; medical menopause is defined as ovarian suppression by any medical cause including treatment with LHRH agonist, radiation, or surgery causing inhibition of pituitary gonadotropin secretion, irrespective of FSH/LH levels.

  Age < 56 years who have medical menopause on LHRH agonist (on stable dose ≥ 1 month) for Phase Ib Cohorts D1, D2, and C3
- Eastern Cooperative Oncology Group (ECOG) performance status < 2
- Resolution of all acute toxic effects of prior therapy or surgical procedures to baseline or Grade ≤ 1 (except alopecia or other toxicities not considered to be a safety risk for the patient)
- Adequate organ function as defined by the following criteria:

  Absolute neutrophil count (ANC) ≥ 1500/μL

  Platelets ≥ 100,000/μL

  Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 3 times the upper limit of normal (ULN) or AST and ALT ≤ 5 × ULN if liver function abnormalities are due to underlying malignancy or liver metastasis

  Total serum bilirubin ≤ 1.5 × ULN regardless of liver involvement secondary to tumor. Inclusion of patients with increased serum indirect bilirubin (≤ 3 × ULN) due to Gilbert's syndrome is permitted.

  Serum creatinine ≤ 1.5 × ULN

  QTc ≤ 460 msec
- Signed and dated informed consent document indicating that the subject (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment
- Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures

- For women of childbearing potential (including patients with menopause induced by LHRH agonists): agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of LHRH agonist or 28 days after the last dose of GDC-0810 and palbociclib (whichever is latest)

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Additional inclusion criteria for Cohorts C0, C1, C2, and C3 (palbociclib combination cohorts): No prior treatment with CDK4/6 inhibitor

<u>Phase Ib Exclusion Criteria</u>

- Untreated or symptomatic CNS metastases.

  Note: Patients with treated and asymptomatic CNS metastases that are radiographically stable within 12 weeks prior to enrollment will be allowed, provided long-term use of corticosteroids haves been discontinued within 4 weeks prior to enrollment.
- Patients with a history of endometrial polyps, endometrial cancer, atypical endometrial hyperplasia, or other significant endometrial disorders should be excluded unless they have undergone total hysterectomy and there is no evidence of active disease.
- More than two prior chemotherapies including adjuvant chemotherapy
- Current treatment with any systemic anti-cancer therapies for advanced disease or any systemic experimental treatment on another clinical trial
- Diagnosis of any secondary malignancy within 2 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ
- Any of the following within 12 months prior to enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of Grade ≥ 2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, or cerebrovascular accident including transient ischemic attack
- Active inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), any active bowel inflammation (including diverticulitis), chronic diarrhea, short bowel syndrome, or history of upper gastrointestinal surgery including gastric resection
- Known human immunodeficiency virus (HIV) infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., hepatitis B or hepatitis C virus), current alcohol abuse, or cirrhosis
- Major surgery within 4 weeks prior to enrollment
- Radiation therapy within 2 weeks prior to enrollment
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study
- Pregnancy, lactation, or breastfeeding

- Additional exclusion criteria for patients in Cohorts C0, C1, C2 or C3 (palbociclib combination cohorts)

    History of venous thromboembolic event requiring therapeutic anticoagulation

    Vaginal bleeding within 2 months prior to enrollment

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs*, GDC-0810 drug supply is exhausted, or when Sponsor decides to stop the study.*

Length of Study

Study duration will be from April 2013 to *when GDC-0810 drug supply is exhausted, or when Sponsor decides to stop the study.*

Investigational Medicinal Products

The research staff at each participating site will provide detailed instructions and training for the handling of the study drug (GDC-0810) and study treatment (palbociclib) and their administration to each patient at the beginning of her study participation.

All patients should take the full prescribed dose of GDC-0810 by mouth at approximately the same time each day and within 30 minutes after eating a meal. GDC-0810 tablets should be swallowed whole and tablets should not be cut or crushed.

Evening dosing may be initiated to alleviate gastrointestinal symptoms from GDC-0810. Please note that morning dosing the day before PK evaluation days is required to allow accurate assessment of PK trough levels of study drug.

If a dose is missed, patients should just take the next scheduled GDC-0810 dose, without compensating for the missed dose.

Palbociclib (Phase Ib Cohorts C0 *and* C1): Refer to palbociclib package insert for details on the formulation and storage of palbociclib. Palbociclib will be *supplied* by the Sponsor.

Phase Ia

During Phase Ia, the full prescribed dose of GDC-0810 should be taken by mouth in the morning, after fasting overnight, at approximately the same time each day; food should not be eaten for at least 1 hour after taking GDC-0810. The dosing regimen may be changed if the PK and safety data from the dose escalation suggest that a discontinuous regimen or another dosing frequency (e.g., BID), with or without a fasting requirement, may be preferable for the Phase IIa portion of the study.

PK Week Lead-In: In Phase Ia, patients enrolled in the dose escalation cohorts will receive a single oral dose of GDC-0810 in the clinic on Day –7 and will return to the clinic for the next 2 consecutive days for PK sample collection. The time of dose administration will be called "0" (zero) hour. If a patient vomits after receiving GDC-0810, this should be recorded in the patient's Case Report Form (CRF) but the dose should not be repeated.

In Phase Ib and Phase IIa, there will be no Day – 7 to Day 0 PK lead-in period.

Continuous Dosing: Phase Ia GDC-0810 will be given continuously beginning on Cycle 1 Day 1 in 28-day cycles. During Cycle 1 of the dose escalation, patients will return to the clinic on a weekly basis (Days 8, 15, and 22) for safety evaluation and collection of predose PK samples. On those days, treatment will be administered in the clinic.

Similarly, on Day 1 of every subsequent new cycle of dosing beginning with Cycle 2, study drug will be administered in the clinic following all the assessments as indicated in the Schedule of Activities.

All other doses of GDC-0810 will be administered on an outpatient basis. It is anticipated that some patients may occasionally forget to take a dose of GDC-0810. In those cases, patients should just take the next scheduled dose, without compensating for the missed dose.

Phase IIa

The full bed dose of GDC-0810 should be taken by mouth at approximately the same time each day and within 30 minutes after eating a meal.

Phase Ib

Palbociclib administration (if applicable): Palbociclib should be taken with food at the same time each day. The capsule should be swallowed whole. The capsules should not be chewed, crushed, or opened. If a dose is missed, patients should just take the next scheduled palbociclib dose, without compensating for the missed dose.

LHRH administration (if applicable): LHRH agonists should be administered monthly by site staff.

Continuous Dosing: In Phase Ib, GDC-0810 will be given continuously beginning on Cycle 1 Day 1 in 28-day cycles. During Cycle 1 of the dose escalation, patients will return to the clinic on a weekly basis (Days 8, 15, and 22) for safety evaluation and collection of predose PK samples. On those days, treatment will be administered in the clinic. Study treatments, palbociclib will be given on Days 1–21 of each cycle and LHRH agonist will be given on Day 1 of each cycle. Evening dosing may be initiated to alleviate gastrointestinal symptoms from GDC-0810. However, on Day 28 of Cycles 1, 2, and 3, the dose of GDC-0810 should be taken in the morning to allow trough PK sample collections on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1.

Similarly, on Day 1 of every subsequent new cycle of dosing beginning with Cycle 2, study treatment will be administered in the clinic following all the assessments as indicated in the Schedule of Activities.

All other doses of GDC-0810 or palbociclib will be administered on an outpatient basis. It is anticipated that some patients may occasionally forget to take a dose of GDC-0810 or palbociclib. In those cases, patients should just take the next scheduled dose, without compensating for the missed dose.

Non-Investigational Medicinal Products

Luteinizing Hormone Releasing Hormone Agonist (LHRH) (Phase Ib Cohort D1): Choice of LHRH agonist will be an institutional choice approved for use in breast cancer. Refer to LHRH agonist package insert for details on the formulation and storage of LHRH agonist. If patient becomes intolerant to current LHRH agonist, then patient may switch to another approved LHRH agonist during trial. LHRH agonists will be prescribed by the study sites and cost of the study treatment will be reimbursed by the Sponsor for the duration of the study.

Statistical Methods

Primary Analysis

Phase Ia and Phase Ib

For safety analyses, the analysis population will include all enrolled patients who receive at least one dose of study medication.

Study treatment discontinuation and reasons for patient discontinuations from the study will be described and summarized. Study drug administration data will be listed and any dose modifications will be flagged.

Phase IIa

Disease assessments (CT scan of the chest, abdomen, and pelvis, plus a bone scan) will be performed at screening and every 8 weeks from Cycle 1 Day 1 thereafter, regardless of treatment delays resulting from toxicity. Radiographic confirmation of objective tumor response or disease progression will be based on RECIST v1.1.

Determination of Sample Size

Phase Ia

The number of patients to be enrolled in Phase Ia will depend upon the observed safety and PK/PD profile, which will determine the number of dose escalations.

Phase IIa

At the RP2D, a total of approximately 100 patients *have been* enrolled to further assess the safety, tolerability, preliminary evidence of anti-tumor activity, and exploratory PD markers of response of GDC-0810 in 3 distinct patient populations (Cohorts A1 and A2 will be combined for analysis purposes).

Phase Ib

Approximately *5* patients *have been* enrolled in the Phase Ib dose escalation cohorts (Cohorts C0 *and* C1). *No additional patients will be enrolled.*

LIST OF ABBREVIATIONS

Abbreviation	Definition
21/7	21/7 = Days 1–21 of 28-day cycle (no dosing holiday)
28/7	28/0 = Days 1–28 of 28-day cycle (no dosing holiday);
AE	adverse event
AI	aromatase inhibitor
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
BID	bis en die (twice daily)
CBC	complete blood count
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CRF	case report form
CSF	colony stimulating factors
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DLT	dose-limiting toxicity
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
ER	estrogen receptor
ESR1	ER-α
FDA	U.S. Food and Drug Administration
FES-PET	fluoroestradiol positron emitting tomography
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
HER2	human epidermal growth factor 2
HIPAA	Health Insurance Portability and Accountability Act of 1996
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IMP	investigational medicinal product

Abbreviation	Definition
IRB	Institutional Review Board
IV	intravenous
LBD	ligand-binding domain
LHRH	luteinizing hormone-releasing hormone
LPLV	last patient last visit
mBC	metastatic breast cancer
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response rate
PD	pharmacodynamic
PET	positron emitting tomography
PGx	pharmacogenomic
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PK	pharmacokinetic
PO	by mounth
QD	once daily
Q4W	every 4 weeks
QTc	corrected QT interval
Rb	retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase II dose
SAE	serious adverse event
SERD	selective estrogen receptor down-regulator
SHBG	sex hormone-binding globulin
SOC	system organ class
T_{max}	time of maximal plasma concentration
ULN	upper limit of normal
VTE	venous thromboembolism

1. BACKGROUND ON ESTROGEN RECEPTOR POSITIVE BREAST CANCER

Breast cancer is the most common form of cancer and the leading cause of cancer death in women worldwide, accounting for more than 1,300,000 new cases and nearly 500,000 cancer deaths annually (Jemal et al. 2011). Approximately 80% of all breast cancers express and are dependent on the estrogen receptor (ER) for tumor growth and progression. Modulation of estrogen activity and/or synthesis is the mainstay of the therapeutic approach in women with ER-positive (ER+) breast cancer. However, despite the effectiveness of available hormonal therapies such as tamoxifen, aromatase inhibitors (AIs; e.g., anastrozole, letrozole, and exemestane), and full ER antagonists/degraders (e.g., fulvestrant), many patients ultimately relapse or develop resistance to these agents and therefore require further treatment for optimal disease control. As such, there is a need for the development of new ER-targeting therapies with increased anti-tumor activity to further delay disease progression and/or overcome resistance to the currently available hormonal therapies and ultimately prolong survival in women with ER+ advanced breast cancer.

Despite becoming refractory to AIs or tamoxifen, growth and survival of resistant tumor cells remain dependent on ER signaling; therefore, patients with ER+ breast cancer can still respond to second-/third-line hormonal treatment after progression on prior hormonal therapy (Di Leo et al. 2010; Baselga et al. 2011). Importantly, there is growing evidence that in the endocrine resistant state, ER can signal in a ligand-independent manner (Miller et al. 2010; Van Tine et al. 2011). An agent with a dual mechanism of action (ER antagonism plus degradation) has the potential to target both ligand-dependent and independent ER signaling and, consequently, improve treatment outcomes in late stage ER+ breast cancer. Furthermore, recent studies have identified mutations in ER-α (ESR1) affecting the ligand-binding domain (LBD) of the ER. Mutant receptors drive ER-dependent transcription and proliferation in the absence of estrogen and reduce the efficacy of ER antagonists, suggesting that LBD-mutant forms of ER are involved in mediating clinical resistance to endocrine therapy and that more potent ER antagonists may be of substantial therapeutic benefit (Li et al. 2013; Robinson et al. 2013; Toy et al. 2013).

Background on GDC-0810

The term "study drug" will be used throughout the protocol to refer to GDC-0810. GDC-0810 is a novel, potent ER-α antagonist that *was* being developed for use as a single agent or in combination with other anti-cancer therapies as treatment for ER+ advanced breast *cancer. The development of GDC-0810 has been halted as a result of a Sponsor decision to evaluate strategic options for this molecule. The decision to halt the development of GDC-0810 is not due to any safety concerns. No further patients will be enrolled into GDC-0810 studies.*

GDC-0810 is a small-molecule therapeutic agent that competes with estrogens for binding to the ER with low nanomolar potency. *In MCF-7 breast cancer cells, the activity of GDC-0810 differentiates from that of first generation ER antagonists, such as tamoxifen, fully antagonizing the response of ER to estrogens and inducing proteosomal degradation of ERα. In other ER+ breast cancer cell lines, such as HCC1500, MDA-MB-330, and Cama1 cells, GDC-0810 attenuates the transcriptional and proliferative response of ER to estrogens without inducing significant ERα degradation. GDC-0810 has a non-steroidal structure and displays good oral bioavailability in all nonclinical species tested, unlike fulvestrant, which has a steroidal structure and exhibits poor bioavailability.*

Summary of Nonclinical Data

GDC-0810 is a potent ER-α antagonist resulting in robust inhibition of ER signaling and *inhibition of* breast tumor cell proliferation. In vivo, GDC-0810 exhibited dose dependent anti-tumor activity in both tamoxifen-sensitive and tamoxifen-resistant *MCF7* xenograft models of ER+ breast cancer. In all models, the efficacious dose range was 10–100 mg/kg/day, and all doses were well tolerated. Efficacy in tamoxifen-resistant xenograft models correlated with efficient antagonist activity on ER target genes and reduction of ER-α tumor levels. *F*ulvestrant appeared to be less efficacious than GDC-0810 in these models.

1.1 GDC-0810 SINGLE AGENT CLINICAL SAFETY SUMMARY

As of 1 October 2014, enrollment in the Phase I dose-escalation portion of the study was completed with 41 patients enrolled at doses from 100 mg to 800 mg.

As of *15 April 2016*, one of 6 patients had experienced a dose-limiting toxicity (DLT) of Grade 3 diarrhea in the 800-mg once daily (QD) fasting cohort, which resolved with dose modification and antidiarrheal therapy. A maximum tolerated dose (MTD) was not determined. However, given the high proportion of gastrointestinal (GI) adverse events, doses of 800 mg were deemed intolerable in the clinical setting of breast cancer. A recommended Phase II dose (RP2D) of 600 mg QD administered under fed conditions (i.e., 30 minutes after eating a meal) was selected based on the overall safety/tolerability and pharmacokinetic (PK) profile of GDC-0810.

As of *15 April 2016*, adverse events of any grade related to study drug occurring at >20% frequency in the Phase I*a* study were diarrhea (76%), nausea (*66*%), fatigue (*59*%), vomiting (34%), decreased appetite *(29%),*flatulence (27%), *abdominal pain (24%),* anemia (24%), dyspepsia (24%), *hot flushes (24%), hypertriglyceridaemia (24%),* muscle spasms (24%)*, and aspartate aminotransferase increase (22%)* (n=41 patients treated at doses from 100 mg to 800 mg). Diarrhea was mostly Grade 1, intermittent in nature, and manageable with dose modifications, dietary adjustments, and treatment with loperamide as needed. As of *15 April 2016*, the median treatment duration is 123 days (range 28–*790* days) for patients in the Phase Ia study.

As of *9 September 2016*, *107* patients have been enrolled in the *combined Phase Ib Cohort D1 and* Phase IIa dose-expansion portion of Study GO29642. *Phase IIa investigated GDC-0810* at the RP2D of 600 mg QD administered within 30 minutes after a meal. *Phase Ib Cohort D1 investigated 600 mg of GDC-0810 in combination with a luteinizing hormone-releasing hormone (LHRH) agonist. Six patients were enrolled in Cohort D1, thus the 107 patients are predominantly from the Phase IIa portion of Study GO29642,* Adverse events of any grade related to study drug occurring at >20% frequency in the Phase IIa study were diarrhea (*44*%), nausea *(38%),* fatigue (*36*%), and hot flush (21%). Administering GDC-0810 within 30 minutes after a meal may have lowered the incidence of GI toxicities (diarrhea, nausea, vomiting) observed in Phase IIa, compared *with* the Phase Ia experience with GI toxicities when GDC-0810 was administered under fasting or non-fasting conditions. Safety data for the Phase IIa study remain preliminary with the median treatment duration being *77* days (range 1*–547* days).

As of 9 September 2016, 4 patients had been enrolled in the Phase 1b dose-escalation combination Cohort C1 that examined GDC-0810 at 400 mg in combination with palbociclib at 125 mg. Adverse events of any grade related to study drug occurring at >20% frequency in Cohort C1 were diarrhea (50%), nausea (75%), fatigue (50%), hot flush (25%), decreased appetite (25%), and gastrooesophageal reflux disease (25%). Safety data for Cohort C1 remain preliminary with a median treatment duration of 134 days (range 56–138 days),

As of *9 September 2016*, among potential risks of GDC-0810, regardless of relatedness, no cases of endometrial cancer *or* phototoxicity were reported in either portion of Study GO29642. *Acute renal failure was reported in 2 (1.3%) patients across all phases of Study GO29642 (combined n=148), neither case was considered related to GDC-0810.* Regardless of relatedness, *9* (*6.1*%) venous thromboembolic *events* (VTE*s*) were reported across *all* phases of Study GO29642. *Adverse event terms were pulmonary embolism and deep vein thrombosis.* Grades *ranged* between 2 and 4. All patients were successfully anti-coagulated following diagnosis of their thromboses. As described in the Investigator's Brochure*, Version 4 (January 2017), the only identified risks for GDC-0810 are diarrhea, vomiting, and nausea. For a full discussion of the adverse event profile of GDC-0810, refer to Section 6 of the Investigator's Brochure.*

Adverse events observed for GDC-0810 thus far are similar to those that have been observed with other endocrine agents and are amenable to monitoring, *are* manageable, and *are* reversible.

1.2 CLINICAL PK SUMMARY

The clinical pharmacokinetics of GDC-0810 is under investigation in the ongoing clinical Phase Ia/IIa Study GO29642. Preliminary PK information from this study is summarized below.

- GDC-0810 was rapidly absorbed with peak concentrations achieved at 1–3 hours after dosing.
- The mean terminal half-life was approximately 8 hours, and mean apparent oral clearance was 8 L/hour after a single dose of GDC-0810 at 600 mg under the non-fasted condition. Consistent with the half-life, minimal drug accumulation was observed following multiple dosing.
- GDC-0810 exposure in the fasted state increased with dose across the entire dose range tested (100–800 mg).
- In the Phase Ia *portion of the study*, at 600 mg QD, mean ± SD steady state AUC_{0-6} and C_{max} for GDC-0810 was 41.1 ± 27.5 μg • hour/mL and 11.8 ± 6.61 μg/mL, respectively, under the fasted state (n=6), and 74.9 ± 30.1 μg • hour/mL and 25 ± 8.35 μg/mL, respectively, under the nonfasted state (n=5).
- In the Phase IIa *portion of the study*, at the RP2D of 600 mg QD under the fed state, mean ± SD steady state AUC_{0-6} and C_{max} for GDC-0810 was 39.5 ± 22.5 μg • hour/mL (n=40) and 14.3 ± 7.3 μg/mL (n=42), respectively.

Based on pharmacodynamic (PD), clinical tolerability, and preliminary PK data collected to date, once-daily administration of 600 mg under fed conditions (within 30 minutes after eating a meal) was selected as the single-agent RP2D for GDC-0810. See the GDC-0810 Investigator Brochure for further details.

2. BACKGROUND ON CYCLIN-DEPENDENT KINASES AND PALBOCICLIB (IBRANCE)

Cyclin-dependent kinases (CDKs) are key regulators of cell cycle progression. The cyclin D-CDK4/6 pathway is involved in promoting the transition from G1 phase to S phase (Musgrove et al. 2011).

CDK4 and CDK6 initiate the phosphorylation of retinoblastoma (Rb) protein, resulting in activation of E2F transcription factors. E2Fs initiate the S phase gene expression program, including the expression of both cyclin E and CDK2, resulting in further Rb phosphorylation and ultimately S phase entry (Malumbres et al. 2009).

Some cancer types disrupt cell cycle progression through loss of RB1 function, making them refractory to the effects of CDK4/6 inhibition (Aarts et al. 2013). In contrast, ER+ breast cancers drive progression through overexpression of cyclin D. Overexpressed cyclin D1 is a common downstream effector of many of the oncogenic drivers of ER+ breast cancer (Finn et al. 2009).

Palbociclib is a highly selective oral inhibitor of CDK4 and CDK6 at low nanomolar concentrations, with 50% inhibitory concentration (IC_{50}) values of 11 nM and 16 nM respectively, that has no inhibitory activity against a panel of 36 additional protein kinases (including CDK1, CDK2 and CDK5) (Fry et al. 2004). It is a reversible, non-ATP competitive inhibitor, which blocks phosphorylation of Rb at serine 780 and serine 795. Palbociclib is anti-proliferative with G1 phase cell arrest in vitro (Turner et al. 2015) and in vivo with activity occurring only in RB1 wild-type cancer models (Fry et al. 2004).

2.1 NONCLINICAL OVERVIEW OF PALBOCICLIB

Palbociclib is anti-proliferative, inhibits cellular DNA syntheses by preventing S phase entry, and specifically causes G1 cell cycle arrest in Rb-positive cells. In Rb-positive cancer cell lines including breast, colon, and lung carcinomas, palbociclib inhibited thymidine incorporation into DNA. These effects of palbociclib were not observed in Rb-deficient cell lines such as MDA-MB-468 human breast carcinomas (Fry et al. 2004).

In vitro, palbociclib reduced cellular proliferation of ER+ breast cancer cell lines by blocking progression from G1 to S phase of the cell cycle. Treatment of breast cancer cell lines with the combination of palbociclib and tamoxifen was synergistic in vitro with more than additive effects on growth arrest compared to treatment with each drug alone (Finn et al. 2009).

Bazedoxifene, a selective estrogen modulator, in combination with palbociclib is efficacious in an ESR1 mutant (Y537S) PDX model (Wardell et al. 2015). Furthermore, AZD9496, an oral selective estrogen receptor down-regulator (SERD) in Phase I development, demonstrated tumor regressions in combination with palbociclib in vivo (De Savi et al. 2015).

2.2 CLINICAL OVERVIEW OF PALBOCICLIB

Palbociclib is being evaluated in many cancer types including breast, ovarian, gastrointestinal stromal tumors (GIST), liposarcomas, acute leukemias, and mantle cell lymphomas.

The DLT of palbociclib is reversible myelosuppression, specifically reversible neutropenia (Gr 1–2: 33–54%; Gr 3–4: 20–50%). Other hematological toxicities include thrombocytopenia (Gr 1–2: 7–58%; Gr 3–4: 0–17%) and anemia (Gr 1–2: 20–64%; Gr 3–4: 2–17%). Phase I and II clinical trials demonstrate that palbociclib is a well-tolerated agent with mild to moderate fatigue (10–34%), nausea (24–30%), and diarrhea (1–30%) as the most commonly reported non-hematological adverse reactions (Schwartz et al. 2011; Flaherty et al. 2012; Dickson et al. 2013; Vaughn et al. 2015). Grade 3 and Grade 4 febrile neutropenia occurred in one of 30 patients (3%) in the two single-agent Phase II studies, respectively (Dickson et al. 2013; Vaughn et al. 2015).

The PALOMA-1 Phase II study randomized women with advanced ER+ human epidermal growth factor 2 (HER2–) breast cancer who had not received any systemic

treatment for their advanced disease to receive either letrozole 2.5 mg QD alone or with palbociclib 125 mg QD administered daily for 21 days followed by a seven day off-period (21/7). The most common adverse events reported for the palbociclib plus letrozole group were neutropenia (74%), leukopenia (43%), fatigue (40%), anemia (35%), and nausea (25%). Grade 3 treatment-related adverse events (AEs) reported in ≥20% of patients were neutropenia (48%) and leukopenia (19%). There were no cases of febrile neutropenia reported. The most frequently reported Grade 4 adverse events were neutropenia (6%), pulmonary embolism (5%), and fatigue (2%). The results showed substantial efficacy with the palbociclib and letrozole combination by significant improvement in median progression-free survival of 20 months (95% CI: 13.8, 27.5 months) compared to letrozole alone (10.2 months; 95% CI: 5.7, 12.6 months) (Finn et al. 2009). Palbociclib received accelerated approval from the United States Food and Drug Administration (FDA) in 2015.

In the randomized Phase III study (PALOMA-3), pre- and postmenopausal women with ER+ (HER2)-breast cancer that relapsed or progressed on endocrine therapy received palbociclib in combination with fulvestrant or placebo and fulvestrant. The median progression-free survival was 9.2 months (95% CI: 7.5 months, not estimable) with palbociclib and fulvestrant, and 3.8 months (95% CI: 3.5, 5.5 months) with placebo and fulvestrant. *Hematological adverse events were more common in the fulvestrant plus palbociclib arm compared with the fulvestrant plus placebo arm, including neutropenia (81% vs. 3%), leucopenia (50% vs. 4%), anaemia (28% vs. 11%), and thrombocytopenia (21% vs. 0%). Anaemia and thrombocytopenia were predominantly Grade 1 to 2 in the palbociclib arm. Neutropenia (Grade ≥3 was 65%) and leucopenia (Grade ≥3 was 28%) were predominantly a higher grade in the palbociclib arm. Whereas infections were more common in the palbociclib arm than the placebo arm (42% vs 30%), these were predominantly Grade 1 to 2 in severity with only 2% of patients in the palbociclib arm experiencing infections of Grade ≥3 compared with 3% in the placebo arm. Febrile neutropenia was rare in both arms at 1% each (all events were Grade ≥3 in each arm with no Grade 5 events in either arm). Common non-hematological events for the palbociclib and placebo arms, respectively, included fatigue (39% vs. 28%), nausea (32% vs. 28%), headache (24% vs. 19%), diarrhea (21% vs. 19%), and vomiting (17% vs. 15%) (Cristofanilli et al. 2016).*

Thromboembolic events have been reported in patients receiving palbociclib. In the PALOMA-3 study of palbociclib in combination with fulvestrant, pulmonary embolism was reported in three patients receiving palbociclib (0.9%) compared with no patients receiving placebo (*Cristofanilli et al. 2016*). In the PALOMA-1 study of palbociclib in combination with letrozole, pulmonary embolism was reported in 5% of patients compared with no cases in the letrozole alone arm (Finn et al. 2016).

2.3 BACKGROUND ON OVARIAN ABLATION AND LHRH AGONIST

Peri- and premenopausal women comprise approximately 20% of patients with metastatic breast cancer and constitute a group with high unmet need of additional therapy options. Ovarian ablation methods for peri- and premenopausal women include surgical oophorectomy, ovarian irradiation, and treatment with LHRH agonists; the latter initially stimulate the production of estrogen in a non-pulsatile/non-physiological manner, causing disruption of the endogenous hormonal feedback systems, which results in the down-regulation of estrogen production. LHRH agonists have been combined with endocrine therapies without significantly affecting their respective safety profiles in adjuvant and metastatic settings, as demonstrated in studies such as such as SOFT/TEXT (LHRH agonist combined with exemestane or tamoxifen) and PALOMA-3 (LHRH agonist combined with fulvestrant), respectively (Pagani et al. 2014; Turner et al. 2015). Studies are ongoing to evaluate the selective ER degrader fulvestrant in combination with medical ovarian suppression in premenopausal women with metastatic breast cancer (Samsung Medical Center 2011; Hospital Affiliated to Military Medical Science 2014).

3. STUDY RATIONALE FOR GDC-0810 AS A SINGLE AGENT AND RISK BENEFIT ASSESSMENT

GDC-0810 is a small-molecule therapeutic agent that competes with estrogens for binding to the ER with low nanomolar potency. In murine MCF-7 xenograft models, GDC-0810 has demonstrated robust tumor regression in both tamoxifen-sensitive and tamoxifen-resistant models, with superior tumor growth inhibition to fulvestrant at clinically relevant exposures. *In MCF-7 breast cancer cells, the activity of GDC-0810 differentiates from that of first generation ER antagonists, such as tamoxifen, fully antagonizing the response of ER to estrogens and inducing proteosomal degradation of ERα. In other ER+ breast cancer cell lines, such as HCC1500, MDA-MB-330, and Cama1 cells, GDC-0810 attenuates the transcriptional and proliferative response of ER to estrogens without inducing significant ERα degradation. GDC-0810 has a non-steroidal structure and displays good oral bioavailability in all nonclinical species tested, unlike fulvestrant, which has a steroidal structure and exhibits poor bioavailability.*

As of *15 April 2016*, a total of 41 patients had been treated with GDC-0810 doses ranging from 100–800 mg. Robust ER target engagement across all doses was demonstrated by FES-PET (fluoroestradiol positron emitting tomography) scans. *Sixteen* of *41* (*39*%) evaluable patients in this heavily pre-treated patient population (median 4 prior systemic treatments, range 1–14) had total time on study >6 months, which is comparable to the 24-week clinical benefit rate (CBR) of 32%–42% achieved by fulvestrant in patients with ER+ advanced or metastatic breast cancer (mBC) after one prior endocrine therapy (Chia et al. 2008; Di Leo et al. 2010; Johnston et al. 2013). Additionally, 2 patients with *ESR* mutations have achieved a partial response by

Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 since the data cut at GDC-0810 doses of 300 mg BID and 400 mg twice daily (BID).

At 600 mg by mouth (PO) daily under nonfasting conditions, GDC-0810 was well tolerated. The associated adverse events were largely Grade 1, without need for any dose holds, dose reductions or permanent study drug discontinuations. Diarrhea was the most frequently reported adverse event, occurring in all 6 patients at the 600-mg QD nonfasting dose level (5 patients with Grade 1 and 1 patient with Grade 2 diarrhea), with 2 patients receiving loperamide, and 4 patients not requiring any anti-diarrheal agents. The RP2D chosen for this study is 600 mg PO QD under fed conditions (within 30 minutes after a meal). Based on the nonclinical findings and preliminary clinical findings, the following additional potential safety risks have been highlighted: uterotrophic effects (i.e., endometrial thickening and polyps), VTE effects (e.g., pulmonary embolism, deep vein thrombosis), kidney dysfunction (animal models only), phototoxicity (in-vitro model only), and drug-drug interaction with CYP2C9 substrates (in-vitro model only).

Specific eligibility criteria designed to minimize risk of GI toxicity and other potential risks are included in Section 7, and robust safety monitoring and risk mitigation strategies for all expected or potential safety risks are described in Section *10.4*. The implementation of appropriate dose-modification and treatment guidelines, appropriate choice of inclusion/exclusion criteria, real-time safety monitoring and assessments, and periodic assessment of aggregate safety data and risk/benefit ratio combine to form the monitoring and risk mitigation system.

In summary, the GDC-0810 safety profile remains acceptable and clinical benefit has been observed in patients with refractory ER+ (HER2−) breast cancer.

4. STUDY RATIONALE FOR GDC-0810 IN COMBINATION WITH PALBOCICLIB AND/OR LHRH AGONISTS AND RISK BENEFIT ASSESSMENT

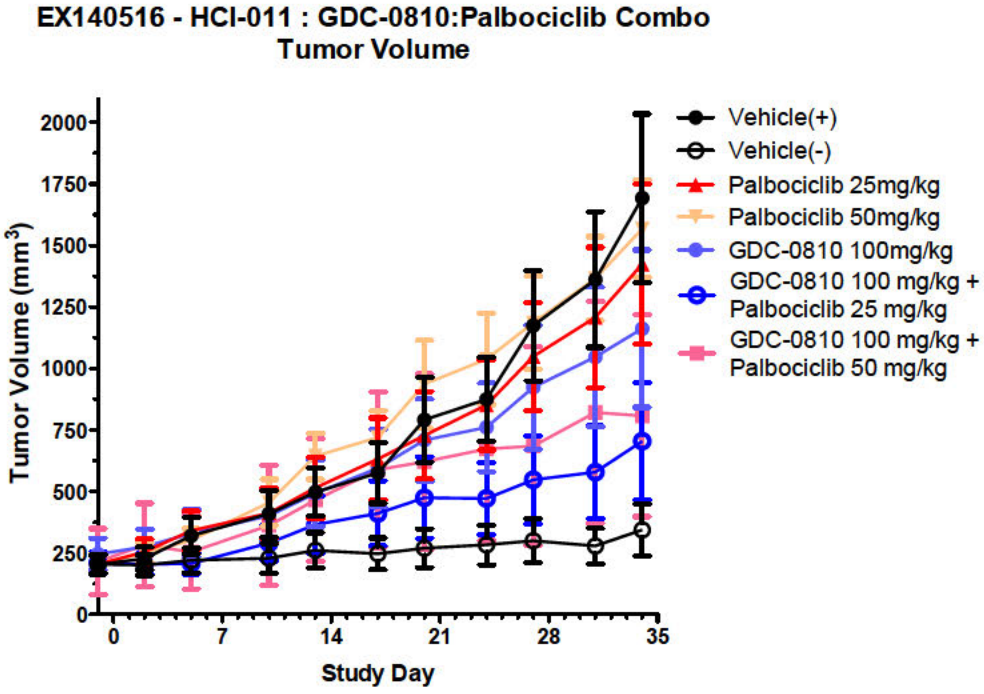
Palbociclib is an orally active selective inhibitor of CDK4/6. The Phase II PALOMA-1 and Phase III PALOMA-3 studies demonstrated the superiority of combining palbociclib with anti-hormonal therapy (letrozole or fulvestrant, respectively) over single agent therapy in first-line and second-line ER+ (HER2−) mBC (Finn et al. 2015; Turner et al. 2015).

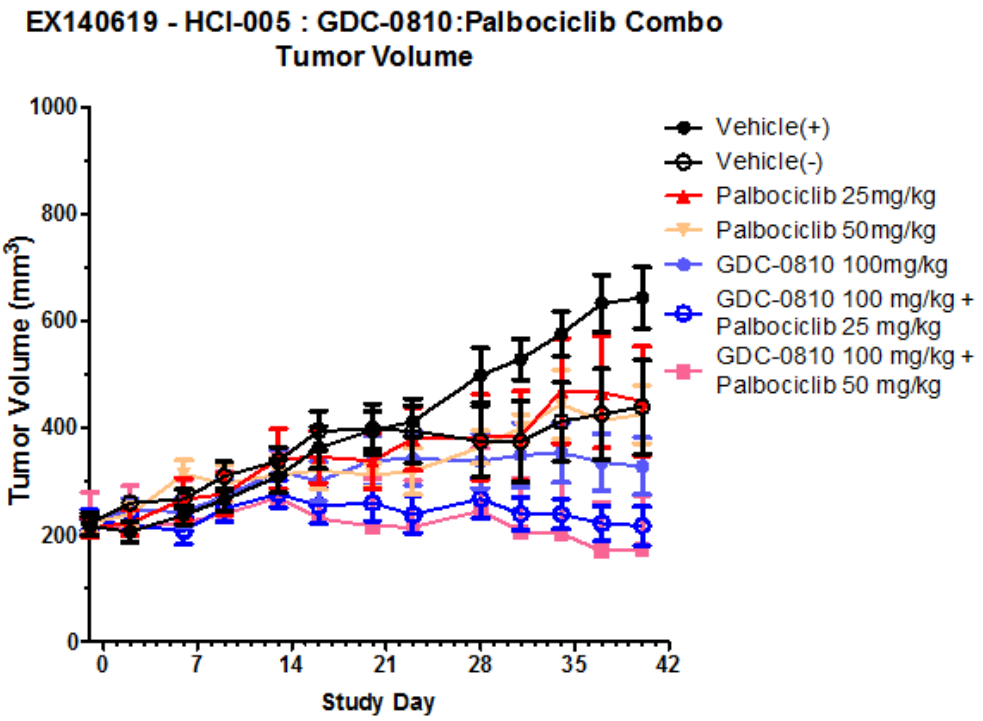
In two ER+ patient−derived xenograft tumor models (HCI-011 and HCI-005, respectively), the combination of GDC-0810 with palbociclib resulted in increased tumor growth inhibition compared with either single agent alone (Figure 1). In clinical trials, the toxicities for palbociclib and GDC-0810 are predominantly non-overlapping. Potential overlapping toxicities include fatigue, nausea, and diarrhea, which are amenable to monitoring, manageable, and reversible. VTE events (including pulmonary embolism)

are an additional potential overlapping toxicity and have been reported in patients receiving single agent GDC-0810 and also in studies involving palbociclib in combination with fulvestrant or letrozole. VTEs have the potential to be life threatening or fatal in intensity but are manageable and reversible if treated. Patients may be educated to be aware of VTE symptoms. It is unknown whether there will be an additive or synergistic risk of VTE from the combination of GDC-0810 and palbociclib.

Overall, the activity of palbocicilb in combination with endocrine therapy observed in patients with advanced ER+ (HER2–) breast cancer (Finn et al. 2015; Turner et al. 2015) warrants the investigation of the combination of GDC-0810 with palbociclib in this group of patients.

Figure 1 Palbociclib: GDC-0810





Vehicle (−) = no estrogen supplementation; Vehicle (+) = 1 mg estrogen supplementation

5. STUDY RATIONALE FOR GDC-0810 IN COMBINATION WITH LHRH AGONIST AND RISK BENEFIT ASSESSMENT

Peri- and premenopausal women, including young women diagnosed with breast cancer before the age of 40, have generally worse prognosis than postmenopausal women (Narod et al. 2012). Peri- and premenopausal women with ER+ (HER2−) breast cancer need more effective endocrine therapy options.

LHRH agonists have been combined with endocrine therapies without significantly affecting their safety profiles in adjuvant and metastatic settings for peri- and premenopausal women (Pagani et al. 2014; Turner et al. 2015). Peri- and premenopausal women are rendered postmenopausal with the LHRH agonists and are able to benefit from endocrine therapies for postmenopausal women. For example, approximately 20% of PALOMA-3 patients were pre- or perimenopausal and demonstrated similar benefit to the overall population (Turner et al. 2015).

5.1 CLINICAL DOSE SELECTION OF PALBOCICLIB

In Cohorts C1 and C2, palbociclib 125 mg will be administered orally on Days 1–21 of a 28-day schedule (Ibrance® [palbociclib] Prescribing Information).

5.2 CLINICAL DOSE SELECTION OF LHRH AGONIST

Enrollment in this study has been discontinued; therefore, no further patients will be enrolled.

In Cohorts D1, D2, and Cohort C3 (in up to 6 patients who will receive GDC-0810, palbociclib and LHRH agonist) LHRH agonist will be administered as a monthly injection on a 28-day schedule. The LHRH agonist will be the physician's choice of an approved LHRH agonist administered according to its respective prescribing information. Dose of LHRH agonist used for study should not deviate from the product's labeled dosage. If patient becomes intolerant to current LHRH agonist, then patient may switch to another approved LHRH agonist during trial.

Peri- and premenopausal women are able to benefit from endocrine therapies for postmenopausal women with the addition of LHRH agonists, which render them postmenopausal but do not have significant additional toxicities (Pagani et al. 2014; Turner et al. 2015). After recommended Phase II dosages of GDC-0810 and palbociclib have been determined from dose escalation cohorts (C1 and C2) and combination of GDC-0810 and LHRH agonists has been shown to be safe (cohort D1), up to 6 pre- and peri-menopausal patients in Cohort C3 will receive LHRH agonist with the RP2D of GDC-0810 in combination with palbociclib. This will enable development of more treatment options for peri- and premenopausal women with breast cancer.

6. STUDY OBJECTIVES

6.1 PRIMARY OBJECTIVES

6.1.1 Phase Ia

- To determine the MTD and/or RP2D and assess the safety of single agent GDC-0810 in postmenopausal women with locally advanced or metastatic ER+ (HER2–) breast cancer

6.1.2 Phase IIa

- To determine the anti-tumor activity of single agent GDC-0810 in postmenopausal women with locally advanced or metastatic ER+ (HER2–) breast cancer

6.1.3 Phase Ib

- To determine the RP2D and assess the safety and tolerability of concomitant administration of GDC-0810 with palbociclib and/or LHRH agonist in women with locally advanced or metastatic ER+ (HER2–) breast cancer

6.2 SECONDARY OBJECTIVES

Phase Ia

- To evaluate the pharmacokinetics of GDC-0810 single agent and its glucuronide metabolites following single and multiple dose treatments.

Phase IIa

- To evaluate the safety of GDC-0810 single agent when administered at the RP2Ds in women with locally advanced or metastatic ER+ (HER2–) breast cancer
- To evaluate the effect of GDC-0810 single agent on ventricular repolarization in postmenopausal women participating in the Phase IIa portion of the study

Phase Ib

- To evaluate the pharmacokinetics of GDC-0810 in combination with palbociclib and/or an LHRH agonist.
- To evaluate the pharmacokinetics of palbociclib and/or an LHRH agonist in combination with GDC-0810

6.2.1 Exploratory Objectives

- To perform exploratory evaluation of biomarkers of PD response with [^{18}F]-fluoroestradiol (FES)-PET in Phase Ia and Phase IIa
- To perform exploratory evaluation of ER target genes
- To perform exploratory evaluation of mechanisms of resistance to GDC-0810

7. STUDY DESIGN

This is a multi-institution Phase Ia/Ib/IIa open-label, dose-finding, safety, PK, and proof-of-concept study of GDC-0810 as a single agent and in combination with palbociclib and/or LHRH agonist.

The study is divided into three phases: Phase Ia, Phase Ib, and Phase IIa *(see Table 1 and Table 2)*. The Phase Ib palbociclib combination cohorts will be conducted in the U.S. only and the LHRH agonists combination cohorts will be conducted in the U.S. and South Korea. The Phase Ia and IIa part of the study (single agent GDC-0810 cohorts) will be conducted in Spain, Netherlands South Korea and the U.S.

Enrollment in Study GO29642 has been discontinued; therefore, no patients will be enrolled in the Phase Ib Cohorts C2, C3, and D2. Any patient currently enrolled in Phase Ia, Ib Cohort C1, Ib Cohort D1, or IIa experiencing clinical benefit may continue to receive GDC-0810 as a single agent or combination with LHRH agonist or palbociclib until disease progression, unmanageable toxicity, patient withdrawal of consent, GDC-0810 drug supply has been exhausted, or the Sponsor terminates the study.

Table 1 Single Agent Cohorts (Phase Ia and IIa)

Phase	Stage	Dose and Schedule	Cohorts
Ia	Dose Escalation	GDC-0810 (28/0)	1–9
IIa	Dose Expansion	GDC-0810 (28/0) at RP2D	A1, A2, B1, B2

28/0 = Days 1–28 of 28-day cycle (no dosing holiday); RP2D = recommended Phase II dose.

Table 2 Combination Cohorts (Phase Ib)

Phase	Stage	Dose and Schedule	Cohorts
Ib	Dose Escalation	400 mg GDC-0810 (28/0) + 100 mg Palbociclib (21/7)	C0[b]
Ib	Dose Escalation	400 mg GDC-0810 (28/0) + 125 mg Palbociclib (21/7)	C1
Ib	Dose Escalation	600 mg GDC-0810 (28/0) + 125 mg Palbociclib (21/7)	C2
Ib	Dose Expansion	GDC-0810 (28/0) at RP3D + 125 mg Palbociclib (21/7)	C3[a]
Ib	Safety Run-in	≤600 mg GDC-0810 (28/0) + LHRH agonist (Q4W)	D1
Ib	Dose Expansion	≤600 mg GDC-0810 (28/0) + LHRH agonist (Q4W)	D2

28/0 = Days 1–28 of 28-day cycle (no dosing holiday); 21/7 = Days 1–21 of 28-day cycle (no dosing holiday); LHRH = luteinizing hormone releasing hormone; Q4W = every 4 weeks.

[a] Up to 6 peri- or premenopausal women may be enrolled in Cohort C3 to receive a combination of GDC-0810 (28/0), LHRH (Q4W), and palbociclib (21/7).

[b] Potential de-escalation cohort

These doses are guidelines only; actual dose escalations or reductions (including different regimens, e.g. 2 weeks on/2 weeks off schedule for palbociclib) may differ and will be determined jointly by Sponsor and study investigators during meetings at which all available safety and PK data will be reviewed prior to dose escalation decisions.

7.1 PHASE IA

Phase Ia consists of dose escalation in postmenopausal women with locally advanced or metastatic ER+ (HER2–) breast cancer *and enrollment into dose escalation cohorts has been completed.*

During Phase Ia, GDC-0810 single agent *was* administered orally to postmenopausal women with locally advanced or metastatic ER+ (HER2–) breast cancer on a continuous daily dosing regimen with a Day –7 lead-in period for single dose PK evaluation prior to the start of daily treatment. The incidence of DLTs will be evaluated from Day –7 through the first cycle (28 days) of treatment (35 days total). Depending on safety and tolerability, patients will be assigned sequentially to escalating doses of GDC-0810 using standard 3+3 design.

The starting dose will be 100 mg once daily. Dosing will be based on flat milligram increments without adjustments for body size. It is anticipated that dose levels will span the anticipated pharmacologically active dose range and be within the safety margin

indicated by nonclinical toxicology studies. The dosing regimen may be changed if the PK and safety data suggest that a discontinuous regimen or another dosing frequency (e.g., BID), with or without a fasting requirement, may be preferable for the Phase IIa portion of the study.

7.2 PHASE IIA

Expansion cohorts consisting of a total of 100 postmenopausal women with locally advanced or metastatic ER+ (HER2−) breast cancer previously treated with an AI will be treated at the RP2D to further characterize the safety, PK, PD, and anti-tumor activity of GDC-0810 as follows:

- **Cohort A:** 30 patients who have confirmed ESR1 mutation of the LBD, further divided into 2 subsets:

  Cohort A1: 20 patients who had **no** prior treatment with fulvestrant. FES-PET will be obtained for PD analysis only in Cohort A1.

  Cohort A2: 10 patients where prior treatment with fulvestrant is allowed

- **Cohort B:** 70 patients who have progressed following ≤1 prior therapy with an AI in the advanced/metastatic setting, further divided into 2 subsets:

  Cohort B1: 50 patients who had **no** prior treatment with fulvestrant

  Cohort B2: 20 patients where prior treatment with fulvestrant is allowed (Figure 2)

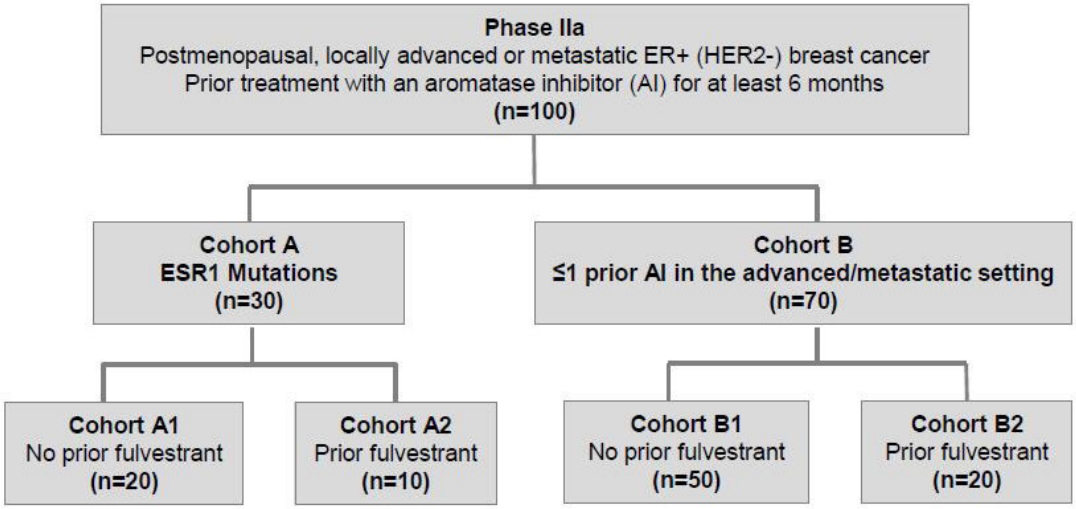
During the Phase Ib and Phase IIa portion of the study, there will be no PK week lead-in period (i.e., all eligible patients will start continuous daily dosing treatment on Cycle 1 Day 1).

The effect of GDC-0810 on ventricular repolarization will be evaluated in all patients enrolled in the Phase IIa portion of the study.

After enrollment is complete in Cohorts A2, B1, and B2 of the Phase IIa portion of the study, further enrollment in Cohort A1 may be discontinued. *Enrollment in the Phase IIa portion of the study is complete.*

All patients will be treated until disease progression, unacceptable toxicity, or patient withdrawal of consent.

Figure 2 Phase IIa Schema

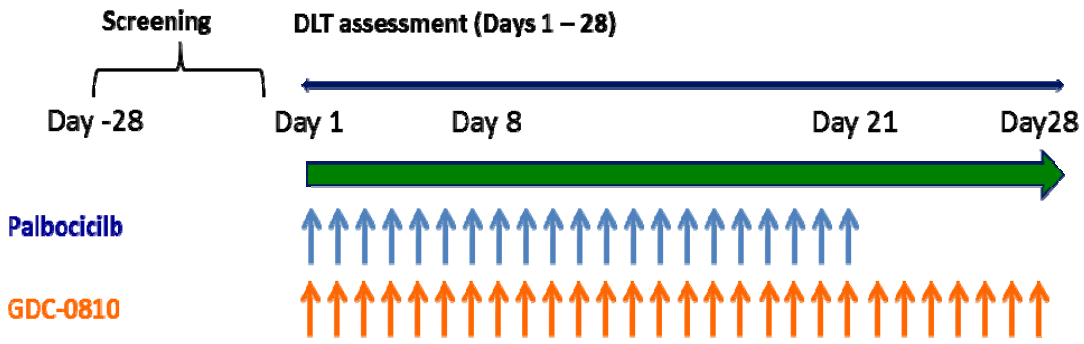


7.3 PHASE IB

Enrollment in Study GO29642 has been discontinued; therefore, no patients will be enrolled in the Phase Ib Cohorts C2, C3, and D2.

In Cohorts C1, C2, and C3 of the Phase Ib study (dose escalation and expansion), GDC-0810 will be administered orally on Days 1–28 of a 28-day schedule and 125 mg palbociclib will be administered on Days 1–21 of a 28-day schedule to women with locally advanced or metastatic ER+ (HER2–) breast cancer (Figure 3). In Cohorts C1 and C2 (dose escalation), patients will be assigned sequentially to escalating doses of GDC-0810 using standard 3+3 design. If the MTD is exceeded at dose level C1 (or the dose level is deemed intolerable in the absence of dose limiting toxicities), de-escalation to dose level C0 may occur. Palbociclib dose de-escalation below 75 mg/day is not allowed, but the schedule may be changed in consultation with the Medical Monitor for example to 75 mg/day 2 weeks on followed by 2 weeks off (2/2 schedule). The starting dose of GDC-0810 will be 400 mg daily, one dose level below the single agent RP2D (Table 2).

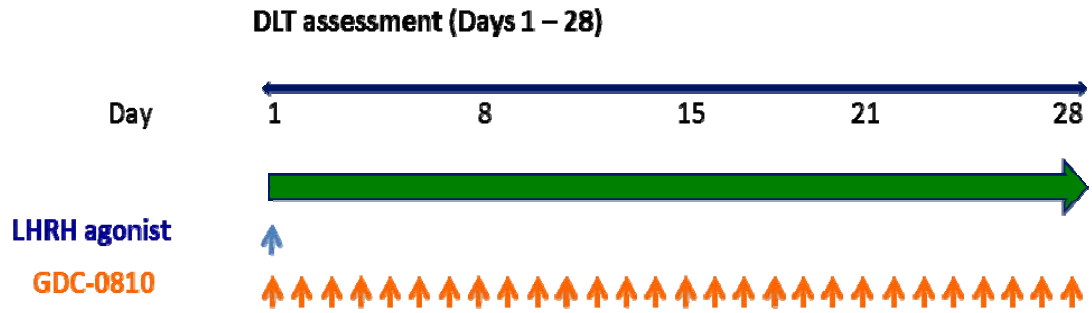
Figure 3 Cohorts C1, C2, and C3 (Dose Escalation and Expansion) Dosing Schema



In Cohort C3, up to 6 pre- or perimenopausal women may be enrolled to receive a combination of GDC-0810 (28/0), LHRH every 4 weeks (Q4W), and palbociclib (21/7).

In Phase Ib Cohort D1 (safety run-in cohort) and Cohort D2 (dose expansion), GDC-0810 will be administered orally on Days 1–28 of a 28-day schedule and an LHRH agonist administered monthly (Figure 4). The GDC-810 dose for Cohort D1 will be 600 mg daily. There will be no dose escalation of either study drug or study drug treatment. *No* patients will be enrolled in Cohort D2.

Figure 4 Cohort D1 (Safety Run-In and Expansion) Dosing Schema



DLT = dose-limiting toxicity; LHRH = luteinizing hormone releasing hormone.

For Cohorts, C0, C1, C2 and D1, the incidence of DLTs will be evaluated from Days 1 to 28 of Cycle 1.

8. PATIENT SELECTION

This study can only fulfill its objectives if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. No waivers or exceptions will be granted for eligibility criteria deviations.

8.1 PHASE IA

8.1.1 Phase Ia Inclusion Criteria

- Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either locally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease, both progressing after at least 6 months of endocrine therapy for ER+ breast cancer
- ER-positive tumor (staining in ≥1% cells by immunohistochemistry [IHC] as per local laboratory testing)
- HER2-negative breast cancer as per local laboratory testing (IHC result of 0 or +1 for cellular membrane protein expression or a fluorescence in situ hybridization [FISH] result showing HER2/CEP17 ratio <1.8 or an average of fewer than 4 copies of *HER2* gene per nucleus for systems without an internal control probe)
- At least 2 months must have elapsed from the use of tamoxifen
- At least 6 months must have elapsed from the use of fulvestrant
- At least 2 weeks must have elapsed from the use of any other anti-cancer hormonal therapy
- At least 3 weeks must have elapsed from the use of any chemotherapy
- Females, 18 years of age or older
- Postmenopausal status defined as:

  Prior bilateral surgical oophorectomy

  Age ≥56 years: natural amenorrhea with ≥1 year since last menses

  Age <56 years with amenorrhea ≥1 year since last menses and serum estradiol levels (<20 pg/mL) and follicle-stimulating hormone (FSH) levels (>40 mIU/mL) in the postmenopausal range

  Age <56 years who had hysterectomy with one or both ovaries left in place, or with tamoxifen-induced amenorrhea together with a tamoxifen discontinuation of ≥1 year and serum estradiol levels (<20 pg/mL) and FSH levels (>40 mIU/mL) in the postmenopausal range

  Age <56 years who have medical menopause on LHRH agonist (on stable dose ≥1 year) with amenorrhea ≥1 year since last menses and serum estradiol levels in the postmenopausal range (<20 pg/mL) irrespective of FSH/LH levels for Phase Ia; medical menopause is defined as ovarian suppression by any medical cause including treatment with LHRH agonist, radiation, or surgery causing inhibition of pituitary gonadotropin secretion, irrespective of FSH/LH levels.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- Resolution of all acute toxic effects of prior therapy or surgical procedures to baseline or Grade ≤1 (except alopecia or other toxicities not considered to be a safety risk for the patient)

- Adequate organ function as defined by the following criteria:

  Absolute neutrophil count (ANC) $\geq 1500/\mu L$

  Platelets $\geq 100{,}000/\mu L$

  Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 3 times the upper limit of normal (ULN) or AST and ALT $\leq 5 \times$ ULN if liver function abnormalities are due to underlying malignancy or liver metastasis

  Total serum bilirubin $\leq 1.5 \times$ ULN regardless of liver involvement secondary to tumor. Inclusion of patients with increased serum indirect bilirubin ($\leq 3 \times$ ULN) due to Gilbert's syndrome is permitted.

  Serum creatinine $\leq 1.5 \times$ ULN

  QTc ≤ 460 msec
- Signed and dated informed consent document indicating that the subject has been informed of all the pertinent aspects of the trial prior to enrollment
- Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures
- For women of childbearing potential (including patients with menopause induced by LHRH agonists): agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 90 days after the last dose of LHRH agonist or 28 days after the last dose of GDC-0810 and palbociclib (whichever is latest)

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of non-hormonal contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

8.1.2 Phase Ia Exclusion Criteria

- Untreated or symptomatic CNS metastases.

  Note: Patients with treated and asymptomatic CNS metastases that are radiographically stable within 12 weeks prior to enrollment will be allowed, provided long-term use of corticosteroids has been discontinued within 4 weeks prior to enrollment.

- Patients with a history of endometrial polyps, endometrial cancer, atypical endometrial hyperplasia, or other significant endometrial disorders should be excluded unless they have undergone total hysterectomy and there is no evidence of active disease.
- More than two prior chemotherapies in the advanced/metastatic setting (prior adjuvant chemotherapy is allowed so long as it occurred ≥ 12 months prior to enrollment)
- Current treatment with any systemic anti-cancer therapies for advanced disease or any systemic experimental treatment on another clinical trial
- Diagnosis of any secondary malignancy within 2 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ
- Any of the following within 12 months prior to enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of Grade ≥ 2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, or cerebrovascular accident including transient ischemic attack
- Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or upper gastrointestinal surgery including gastric resection
- Known human immunodeficiency virus (HIV) infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., hepatitis B or hepatitis C virus), current alcohol abuse, or cirrhosis
- Major surgery within 4 weeks prior to enrollment
- Radiation therapy within 2 weeks prior to enrollment
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study

8.2 PHASE IIa

8.2.1 Phase IIa Inclusion Criteria

- Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either locally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease, both progressing after at least 6 months of endocrine therapy with an aromatase inhibitor for ER+ breast cancer
- ER-positive tumor (staining in ≥ 1% cells by IHC as per local laboratory testing)
- HER2-negative breast cancer as per local laboratory testing (IHC result of 0 or +1 for cellular membrane protein expression or a FISH result showing HER2/CEP17 ratio < 1.8 or an average of fewer than 4 copies of *HER2* gene per nucleus for systems without an internal control probe)

- **Cohort A only:**

  Confirmed ESR1 mutations of the LBD (as determined in a Clinical Laboratory Improvement Amendments [CLIA]-certified laboratory) and consent to provide an archival tumor sample for retrospective confirmation (LBD further defined as the region between ER-α amino acids 302 to 595) and

  Presence of evaluable disease as per RECIST Version 1 further defined as follows:

    Measurable disease, or evaluable bone disease—that is, bone lesions that are lytic or mixed (lytic + sclerotic) in the absence of measurable lesion.
    Note: previously irradiated lesions are deemed measurable only if progression is documented at the site after completion of radiation.

- For patients with soft tissue or visceral metastases that are safely accessible, paired pre- and on-treatment tumor biopsies are required.

  Cohort A1 only: No prior fulvestrant allowed; at least 2 months must have elapsed from the use of tamoxifen (if applicable)

  Cohort A2 only: Prior fulvestrant allowed

- **Cohort B only:** Disease progression following ≤ 1 prior treatment with an AI in the advanced/metastatic setting (prior adjuvant treatment with an AI is allowed):

  Patients must have relapsed ≥ 12 months from completion of adjuvant treatment **or** progressed following ≥ 6 months of treatment in the advanced/metastatic setting.

  Measurable disease, or evaluable bone disease—that is, bone lesions that are lytic or mixed (lytic + sclerotic) in the absence of measurable lesion.
  Note: previously irradiated lesions are deemed measurable only if progression is documented at the site after completion of radiation.

  Cohort B1 only: No prior fulvestrant allowed

  Cohort B2 only: Prior fulvestrant allowed

- At least 2 weeks must have elapsed from the use of the most recent endocrine therapy (for Cohort A1, if most recent endocrine therapy is tamoxifen, see inclusion criterion above)
- At least 3 weeks must have elapsed from the use of any chemotherapy
- Females, 18 years of age or older
- Postmenopausal status defined as:

  Prior bilateral surgical oophorectomy

  Age ≥ 56 years: natural amenorrhea with ≥ 1 year since last menses

  Age < 56 years with amenorrhea ≥ 1 year since last menses and serum estradiol levels (< 20 pg/mL) and FSH levels (> 40 mIU/mL) in the postmenopausal range

Age $<$56 years who had hysterectomy with one or both ovaries left in place, or with tamoxifen-induced amenorrhea together with a tamoxifen discontinuation of $\geq$1 year and serum estradiol levels ($<$20 pg/mL) and FSH levels ($>$40 mIU/mL) in the postmenopausal range

Age $<$56 years who have medical menopause, such as LHRH agonist (on stable dose $\geq$1 year) with amenorrhea $\geq$1 year since last menses and serum estradiol levels in the postmenopausal range ($<$20 pg/mL) irrespective of FSH/LH levels. Cause of medical menopause should be discussed with the Medical Monitor.

- ECOG performance status 0 or 1
- Resolution of all acute toxic effects of prior therapy or surgical procedures to baseline or Grade $\leq$1 (except alopecia or other toxicities not considered to be a safety risk for the patient)
- Adequate organ function as defined by the following criteria:

  Absolute neutrophil count (ANC) $\geq$1500/μL

  Platelets $\geq$100,000/μL

  Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) $\leq 3 \times$ ULN, or AST and ALT $\leq 5 \times$ ULN if liver function abnormalities are due to underlying malignancy or liver metastasis

  Total serum bilirubin $\leq 1.5 \times$ ULN regardless of liver involvement secondary to tumor. Inclusion of patients with increased serum indirect bilirubin ($\leq 3 \times$ ULN) due to Gilbert's syndrome is permitted

  Serum creatinine $\leq 1.5 \times$ ULN

  QTc $\leq$460 msec
- Signed and dated informed consent document indicating that the subject has been informed of all the pertinent aspects of the trial prior to enrollment
- Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures
- For women of childbearing potential (including patients with menopause induced by LHRH agonists): agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods that result in a failure rate of $<$1% per year during the treatment period and for at least 90 days after the last dose of LHRH agonist or 28 days after the last dose of GDC-0810 and palbociclib (whichever is latest).

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of non-hormonal contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation and copper intrauterine devices.

- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

8.2.2 Phase IIa Exclusion Criteria

- Untreated or symptomatic CNS metastases.

  Note: Patients with treated and asymptomatic CNS metastases that are radiographically stable within 12 weeks prior to enrollment will be allowed, provided long-term use of corticosteroids have been discontinued within 4 weeks prior to enrollment

- Patients with a history of endometrial polyps, endometrial cancer, atypical endometrial hyperplasia, or other significant endometrial disorders should be excluded unless they have undergone total hysterectomy and there is no evidence of active disease.
- Prior treatments:

EXCLUSIONS	Prior Endocrine Therapy	Prior Chemotherapy
Cohort A1	▪ Fulvestrant	▪ > 1 prior chemotherapy in the advanced/metastatic setting
Cohort A2		▪ > 1 prior chemotherapy in the advanced/metastatic setting
Cohort B1	▪ > 1 prior AI in the advanced/metastatic setting ▪ Fulvestrant	▪ Prior chemotherapy in the advanced/metastatic setting (prior adjuvant chemotherapy is allowed so long as it occurred ≥ 12 months prior to enrollment)
Cohort B2	▪ > 1 prior AI in the advanced/metastatic setting	▪ > 1 prior chemotherapy in the advanced/metastatic setting

- Current treatment with any systemic anti-cancer therapies for advanced disease
- Diagnosis of any secondary malignancy within 2 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ

- Any of the following within 12 months prior to enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, or cerebrovascular accident including transient ischemic attack
- Active inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), any active bowel inflammation (including diverticulitis), chronic diarrhea, short bowel syndrome, or history of upper gastrointestinal surgery including gastric resection
- Known human immunodeficiency virus infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., Hepatitis B or Hepatitis C virus), current alcohol abuse, or cirrhosis
- Major surgery within 4 weeks prior to enrollment
- Radiation therapy within 2 weeks prior to enrollment
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study

8.3 PHASE IB

8.3.1 Phase Ib Inclusion Criteria

- Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either locally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease
- Documented sensitivity to prior hormonal therapy (relapsed after 24 months of adjuvant endocrine therapy or had a clinical benefit from prior endocrine therapy in the context of advanced disease)
- ER-positive tumor (staining in ≥1% cells by immunohistochemistry [IHC] as per local laboratory testing)
- HER2-negative breast cancer as per local laboratory testing (IHC result of 0 or +1 for cellular membrane protein expression or a FISH result showing HER2/CEP17 ratio <1.8 or an average of fewer than 4 copies of HER2 gene per nucleus for systems without an internal control probe)
- At least 2 weeks must have elapsed from the use of any other anti-cancer hormonal therapy excluding LHRH agonist for patients enrolled in Cohorts C3, D1 and D2
- At least 3 weeks must have elapsed from the use of any chemotherapy
- Females, 18 years of age or older
- Postmenopausal status defined as:

  Prior bilateral surgical oophorectomy

  Age ≥56 years: natural amenorrhea with ≥1 year since last menses

Age <56 years with amenorrhea ≥ 1 year since last menses and serum estradiol levels (<20 pg/mL) and follicle stimulating hormone (FSH) levels (>40 mIU/mL) in the postmenopausal range

Age <56 years who had hysterectomy with one or both ovaries left in place, or with tamoxifen-induced amenorrhea together with a tamoxifen discontinuation of ≥ 1 year and serum estradiol levels (<20 pg/mL) and FSH levels (>40 mIU/mL) in the postmenopausal range

Age <56 years who have medical menopause on LHRH agonist (on stable dose ≥ 1 year) with amenorrhea ≥ 1 year since last menses and serum estradiol levels in the postmenopausal range (<20 pg/mL) irrespective of FSH/LH levels; medical menopause is defined as ovarian suppression by any medical cause including treatment with LHRH agonist, radiation, or surgery causing inhibition of pituitary gonadotropin secretion, irrespective of FSH/LH levels.

Age <56 years who have medical menopause on LHRH agonist (on stable dose ≥ 1 month) for Phase Ib Cohorts D1, D2, and C3

- Eastern Cooperative Oncology Group (ECOG) performance status <2
- Resolution of all acute toxic effects of prior therapy or surgical procedures to baseline or Grade ≤ 1 (except alopecia or other toxicities not considered to be a safety risk for the patient)
- Adequate organ function as defined by the following criteria:

  Absolute neutrophil count (ANC) $\geq 1500/\mu L$

  Platelets $\geq 100{,}000/\mu L$

  Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 3 times the upper limit of normal (ULN) or AST and ALT $\leq 5 \times$ ULN if liver function abnormalities are due to underlying malignancy or liver metastasis

  Total serum bilirubin $\leq 1.5 \times$ ULN regardless of liver involvement secondary to tumor. Inclusion of patients with increased serum indirect bilirubin ($\leq 3 \times$ ULN) due to Gilbert's syndrome is permitted.

  Serum creatinine $\leq 1.5 \times$ ULN

  QTc ≤ 460 msec

- Signed and dated informed consent document indicating that the subject (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment
- Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures
- For women of childbearing potential (including patients with menopause induced by LHRH agonists): agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 90 days after the last dose of LHRH agonist or 28 days after the last dose of GDC-0810 and palbociclib (whichever is latest)

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of non-hormonal contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Additional inclusion criteria for Cohorts C0, C1, C2, and C3 (palbociclib combination cohorts): No prior treatment with CDK4/6 inhibitor

8.3.2 Phase Ib Exclusion Criteria

- Untreated or symptomatic CNS metastases.

  Note: Patients with treated and asymptomatic CNS metastases that are radiographically stable within 12 weeks prior to enrollment will be allowed, provided long-term use of corticosteroids haves been discontinued within 4 weeks prior to enrollment.

- Patients with a history of endometrial polyps, endometrial cancer, atypical endometrial hyperplasia, or other significant endometrial disorders should be excluded unless they have undergone total hysterectomy and there is no evidence of active disease.
- More than two prior chemotherapies including prior adjuvant chemotherapy
- Current treatment with any systemic anti-cancer therapies for advanced disease or any systemic experimental treatment on another clinical trial
- Diagnosis of any secondary malignancy within 2 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ
- Any of the following within 12 months prior to enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, or cerebrovascular accident including transient ischemic attack
- Active inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), any active bowel inflammation (including diverticulitis), chronic diarrhea, short bowel syndrome, or history of upper gastrointestinal surgery including gastric resection
- Known human immunodeficiency virus (HIV) infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., hepatitis B or hepatitis C virus), current alcohol abuse, or cirrhosis
- Major surgery within 4 weeks prior to enrollment
- Radiation therapy within 2 weeks prior to enrollment

- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study
- Pregnancy, lactation, or breastfeeding
- Additional exclusion criteria for patients in Cohorts C0, C1, C2 or C3 (palbociclib combination cohorts)

  History of venous thromboembolic event requiring therapeutic anticoagulation

  Vaginal bleeding within 2 months prior to enrollment

9. STUDY DRUG

The term "study drug" will be used to refer GDC-0810.

9.1 GDC-0810

9.1.1 Description and Composition of the Drug Substance

Chemical Name: (2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-N-methylhexan-1-aminium (E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate

Code Name: GDC-0810 N-Methyl-D-Glucamine (NMG) Salt

Molecular Formula: $C_{33}H_{37}ClFN_3O_7$ ($C_{26}H_{20}ClFN_2O_2 \bullet C_7H_{17}NO_5$)

Molecular Weight: 642.11 Daltons (neutral form 446.90 Daltons)

Appearance: White to yellow to tan crystalline solid

9.1.2 Study Drug Product

GDC-0810 will be provided in two different strengths: 50 mg (8 mm white round tablet containing 50 mg GDC-0810 free acid) and 200 mg (19 mm $\times$ 8 mm white caplet containing 200 mg GDC-0810 free acid). Inactive ingredients include microcrystalline cellulose (Avicel PH101), sodium laurel sulfate, sodium bicarbonate, sodium carboxymethylcellulose (Croscarmellose Sodium), fumed silica (Cab-O-Sil), and magnesium stearate.

9.1.3 Packaging and Labeling

GDC-0810 will be supplied as 50 or 200 mg tablets (depending on total dose levels) packaged in 30-ct, 100 cc HDPE bottles with child-resistant closures and tamper-proof heat induction seals.

Each bottle of study drug will be labeled with the required regulatory agency warning statement, lot number, the Sponsor’s name, and directions for patient use and storage.

10. STUDY TREATMENTS

The term "study treatment" will be used to refer to palbociclib and/or LHRH agonist.

Palbociclib (Cohorts C0 *and* C1)

Refer to palbociclib package insert for details on the formulation and storage of palbociclib. Palbociclib will be *supplied* by the Sponsor. The Sponsor does not intend to provide other study interventions to patients after the conclusion of the study or any earlier withdrawal.

Luteinizing Hormone Releasing Hormone Agonist (LHRH) (Cohort D1)

Choice of LHRH agonist will be an institutional choice approved for use in breast cancer. Refer to LHRH agonist package insert for details on the formulation and storage of LHRH agonist. If patient becomes intolerant to current LHRH agonist, then patient may switch to another approved LHRH agonist during trial. LHRH agonists will be prescribed by the study sites and cost of study treatment will be reimbursed by the Sponsor for the duration of the study. The Sponsor does not intend to provide other study interventions to patients after the conclusion of the study or any earlier withdrawal.

10.1 TREATMENT DOSE ASSIGNMENT

10.1.1 Phase Ia

Standard 3+3 design will be followed for dose-escalation in Phase Ia. The starting dose in Phase Ia of GDC-0810 single agent (Cohorts 1–9) will be 100 mg per day, followed by dose escalation to 200 mg (dose level 2), and by 200 mg increments thereafter (Table 3).

In Phase Ia, a minimum of 3 evaluable patients will be entered at each dose level. If 1 out of the first 3 patients enrolled at any given dose level experiences a DLT, 3 additional patients will be assigned to that dose level. If $\leq$1 patient in 6 experiences a DLT, dose escalation will proceed.

In Phase Ia if $\geq$2 patients at any given dose level experience a DLT, dose escalation will stop and the MTD may be defined as either the previous dose level or upon further evaluation of an intermediate lower dose level (e.g., by 100 mg decrement).

If no DLTs are observed, the RP2D will be based on the overall safety and PK/PD profile of GDC-0810 single agent (Phase Ia), and not necessarily the MTD. The decision to dose escalate or dose reduce will be made during dose escalation data review teleconferences held between the Sponsor and the investigators.

If only 3 patients have been treated at a dose level under consideration as the MTD and/or RP2D, a minimum of 3 additional patients will be treated at that dose level to confirm the MTD and/or RP2D.

In Phase Ia, dose escalation will continue until either of the following has been observed:

The MTD has been exceeded (incidence of DLT ≥33%); or

Pharmacokinetic futility (defined as a lack of increase in exposure with increasing doses of GDC-0810 in at least two successive dose levels) is encountered.

Patients enrolled in Phase Ia will continue treatment at their assigned dose level for at least 2 cycles and observed for cumulative toxicity. After 2 cycles, they may then be treated at the next higher dose level provided it has been shown to be safe (passed the DLT evaluation period) in a previously treated cohort at the discretion of the investigator and in agreement with the patient.

Table 3 Dose Levels for Escalation for Phase Ia (Cohorts 1–9)

Dose Level	GDC-0810
1	100 mg
2	200 mg
3	400 mg [a]
4+	By 200 mg increments from the previous dose

[a] Starting dose of GDC-0810 in Cohort C1 in Phase Ib.

10.1.2 Phase IIa

In the Phase IIa dose-expansion portion of Study GO29642 patients will receive the RP2D of 600 mg QD administered within 30 minutes after a meal.

10.1.3 Phase Ib

10.1.3.1 Cohort C1

GO29642 study enrollment in Phase Ib has been discontinued. No patients will be enrolled in Phase Ib Cohorts C2 and C3.

Standard 3+3 design will be followed for dose-escalation in Cohort C1 of the Phase Ib study.

The starting dose for Phase Ib Cohort C1 dose escalation of GDC-0810 will be 400 mg per day on Days 1–28 of a 28-day schedule, taken together with 125 mg palbociclib administered on Days 1–21 of a 28-day schedule (21/7) (Table 2).

In Cohort C1 of Phase Ib, a minimum of 3 evaluable patients will be entered at each dose level. If 1 out of the first 3 patients enrolled at any given dose level experiences a DLT, 3 additional patients will be assigned to that dose level. If ≤1 patient in 6 experiences a DLT, dose escalation will proceed. If dose level C1 is deemed intolerable in the absence of DLTs, de-escalation to dose level C0 may occur.

In Cohort C1 of Phase Ib, if ≥ 2 patients at any given dose level experience a DLT, dose escalation will stop and the MTD may be defined as either the previous dose level or upon further evaluation of an intermediate lower dose level.

In addition to any DLTs, other available relevant demographic, adverse event, laboratory, dose administration, PK, and PD data will be reviewed prior to all dose escalation decisions.

If no DLTs are observed, the RP2D will be based on the overall safety and PK/PD profile of GDC-0810 and palbociclib, and not necessarily the MTD. The decision to escalate or reduce the dose will be made during dose-escalation data review teleconferences held between the Sponsor and the investigators.

If only 3 patients have been treated at a dose level under consideration as the MTD and/or RP2D, a minimum of 3 additional patients will be treated at that dose level to confirm the MTD and/or RP2D.

Patients enrolled in Cohort C1 of Phase Ib will continue treatment at their assigned dose level for at least 2 cycles and observed for cumulative toxicity. After 2 cycles, they may then be treated at the next higher dose level provided it has been shown to be safe (passed the DLT evaluation period) in a previously treated cohort at the discretion of the investigator and in agreement with the patient.

10.1.3.2 Cohort D1

Study GO29642 enrollment in Phase Ib has been discontinued. No patient will be enrolled in Cohort D2.

Cohort D1 of the Phase Ib study is a safety run-in of 6 patients.

The dose of GDC-0810 in Phase Ib Cohort D1 safety run-in will be 600 mg per day. Dose escalation is not planned for either drug in Cohort D1. However, the dose of GDC-0810 in Cohort D2 may be reduced on the basis of joint review by Sponsor and study investigators of available safety and tolerability data.

In Phase Ib Cohort D1, if 2 or more patients at the combination dose level experience a DLT, evaluation of a lower dose level of GDC-0810 may be initiated.

In addition to any DLTs, other available relevant demographic, adverse event, laboratory, dose administration, PK, and PD data will be reviewed.

If no DLTs are observed, the RP2D will be based on the overall safety and PK/PD profile of and LHRH agonist and not necessarily the MTD. The decision to reduce the dose of GDC-0810 will be made during data review teleconferences held between the Sponsor and the investigators.

10.2 DLT DEFINITION

For DLT evaluation, toxicity will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 4.0) (Appendix 7).

10.2.1 Phase Ia

For Phase Ia, the DLT evaluation period will start from the first dose of GDC-0810 (Day −7) through the first cycle (28 days) of treatment for a total of 35 days.

For Phase Ia, patients who miss 7 or more doses of GDC-0810 during the DLT evaluation period due to reasons other than a DLT will be replaced.

In addition, patients who are discontinued from the study prior to completing the DLT evaluation period, due to reasons other than a DLT (e.g., disease progression, consent withdrawn), will also be replaced.

DLT Definitions

For Phase Ia, DLTs will be defined as any of the following adverse events that are deemed by the investigator or the Sponsor to be related to study drug (toxicities will be attributed to single agent GDC-0810 unless they are clearly related to disease progression or can clearly be attributed to a cause other than GDC-0810 administration):

- Any grade ≥3 non-hematologic toxicity (excluding alopecia)
- Any grade ≥3 hematologic toxicity of >7 days' duration
- Any grade toxicity that leads to study drug interruption of >7 days' duration

10.2.2 Phase IIa

DLT definitions are not applicable for the Phase IIa dose expansion portion of the study.

10.2.3 Phase Ib

No patients will be enrolled in Phase Ib Cohorts C0 and C2.

For Phase Ib Cohorts C0, C1, and D1, the DLT evaluation period will start from Day 1 through Day 28 of Cycle 1.

For Phase Ib, patients who miss ≥7 doses of GDC-0810 or ≥5 doses of palbociclib (in Cohort C0 *or* C1) during the DLT evaluation period due to reasons other than a DLT will be replaced.

Phase Ib Cohorts C0 *and* C1 DLT Definitions

DLT definitions reflect the known and expected toxicities of GDC-0810 administered alone and palbociclib administered alone or in combination with other endocrine therapies. A DLT is defined as one of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to GDC-0810 or palbociclib.

- Any Grade ≥ 3 non-hematologic, non-hepatic toxicity with the exception of:

  Alopecia of any grade;

  Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤ 2 within 24 hours with maximal medical therapy

  Grade 3 fatigue, unless the fatigue has increased by at least two grades from baseline

- Any grade non-hematologic toxicity that leads to study drug or study drug treatment interruption of > 7 days' duration
- Grade ≥ 3 elevation of serum hepatic transaminase (ALT or AST) lasting > 7 days

  For patients with Grade ≤ 2 hepatic transaminase levels at baseline as a result of liver metastases, only a transaminase level $\geq 10 \times$ ULN lasting for > 7 days will be considered a DLT.

- Grade ≥ 3 elevation of serum bilirubin
- Any case of potential drug-induced liver injury that includes an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law as recommended in the U.S. FDA Guidance "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," July 2009:

  The finding of an elevated ALT or AST (> 3 times baseline value) in combination, with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

  Treatment-emergent ALT or AST > 3 times baseline value in combination with clinical jaundice

  Treatment-emergent ALT or AST > 3 times baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)

- Grade 4 febrile neutropenia of any duration
- Grade 4 neutropenia ≥ 10 days
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- Grade 4 thrombocytopenia associated with:

  ≥ 10 days duration

  Active bleeding

  Requirement for platelet transfusion

- Grade 4 anemia

  Note: In the event of a Grade 4 neutropenia, thrombocytopenia, or anemia, a complete blood count (CBC) must be performed at least on Day 5 after the onset of the event. If the absolute neutrophil count, platelet count, or hemoglobin has not recovered to ≤ Grade 3, CBC should be rechecked again on or before Day 10. In order to define DLT, patients should not be prophylactically prescribed growth factor support prior to commencement of therapy (GDC-0810 and palbociclib).

- Grade 3 laboratory abnormalities that are asymptomatic and considered by the investigator not to be clinically significant will not be considered a DLT.

Phase Ib Cohort D1 Dose Safety Run-in DLT Definitions

DLT definitions reflect the known and expected toxicities of GDC-0810 and LHRH agonists. A DLT is defined as one of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to GDC-0810 or LHRH agonists:

- Any Grade ≥ 3 non-hematologic, non-hepatic toxicity with the exception of:

  Alopecia of any grade

  Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤ 2 within 24 hours with maximal medical therapy

  Grade 3 fatigue, unless the fatigue has increased by at least two grades from baseline

  Grade 3 premature menopause or Grade 3 hot flashes that resolve to Grade 2 with optimal medical management within 7 days

  Grade 3 laboratory abnormalities that are asymptomatic and considered by the investigator not to be clinically significant will not be considered a DLT.

- Any Grade ≥ 3 hematologic toxicity of more than 7 days' duration
- Any grade toxicity that leads to study drug or study drug treatment interruption of more than 7 days duration
- Grade ≥ 3 elevation of serum hepatic transaminase (ALT or AST) lasting > 7 days

  For patients with Grade ≤ 2 hepatic transaminase levels at baseline as a result of liver metastases, only a transaminase level ≥ 10 × ULN lasting for ≥ 7 days will be considered a DLT.

- Grade ≥ 3 elevation of serum bilirubin

- Any case of potential drug-induced liver injury that includes an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law as recommended in the U.S. FDA Guidance "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," July 2009:

  The finding of an elevated ALT or AST (>3 times baseline value) in combination, with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

  Treatment-emergent ALT or AST >3 times baseline value in combination with clinical jaundice

  Treatment-emergent ALT or AST >3 times baseline value in combination with total bilirubin $>2\times$ULN (of which $\geq 35\%$ is direct bilirubin)

10.3 STUDY DRUG AND STUDY TREATMENT ADMINISTRATION

The research staff at each participating site will provide detailed instructions and training for the handling of the study drug (GDC-0810) and study treatment (palbociclib and LHRH agonist) and their administration to each patient at the beginning of her study participation.

All patients should take the full prescribed dose of GDC-0810 by mouth at approximately the same time each day and within 30 minutes after eating a meal. GDC-0810 tablets should be swallowed whole and tablets should not be cut or crushed.

Evening dosing may be initiated to alleviate gastrointestinal symptoms from GDC-0810. Please note that morning dosing the day before PK evaluation days is required to allow accurate assessment of PK trough levels of study drug (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

If a dose is missed, patients should just take the next scheduled GDC-0810 dose, without compensating for the missed dose.

10.3.1 Phase Ia

During Phase Ia, the full prescribed dose of GDC-0810 should be taken by mouth in the morning, after fasting overnight, at approximately the same time each day; food should not be eaten for at least 1 hour after taking GDC-0810. The dosing regimen may be changed if the PK and safety data from the dose escalation suggest that a discontinuous regimen or another dosing frequency (e.g., BID), with or without a fasting requirement, may be preferable for the Phase IIa portion of the study.

PK Week Lead-In

In Phase Ia, patients enrolled in the dose escalation cohorts will receive a single oral dose of GDC-0810 in the clinic on Day -7 and will return to the clinic for the next 2 consecutive days for PK sample collection. The time of dose administration will be

called “0” (zero) hour. If a patient vomits after receiving GDC-0810, this should be recorded in the patient’s Case Report Form (CRF) but the dose should not be repeated.

In Phase Ib and Phase IIa, there will be no Day −7 to Day 0 PK lead-in period.

Continuous Dosing

In Phase Ia GDC-0810 will be given continuously beginning on Cycle 1 Day 1 in 28-day cycles. During Cycle 1 of the dose escalation, patients will return to the clinic on a weekly basis (Days 8, 15, and 22) for safety evaluation and collection of predose PK samples. On those days, treatment will be administered in the clinic.

Similarly, on Day 1 of every subsequent new cycle of dosing beginning with Cycle 2, study drug will be administered in the clinic following all the assessments as indicated in the Schedule of Activities.

All other doses of GDC-0810 will be administered on an outpatient basis. It is anticipated that some patients may occasionally forget to take a dose of GDC-0810. In those cases, patients should just take the next scheduled dose, without compensating for the missed dose.

10.3.2 Phase IIa

The full prescribed dose of GDC-0810 should be taken by mouth at approximately the same time each day and within 30 minutes after eating a meal.

10.3.3 Phase Ib

Palbociclib administration (if applicable): Palbociclib should be taken with food at the same time each day. The capsule should be swallowed whole. The capsules should not be chewed, crushed, or opened. If a dose is missed, patients should just take the next scheduled palbociclib dose, without compensating for the missed dose.

LHRH administration (if applicable): LHRH agonists should be administered monthly by site staff.

Continuous Dosing

In Phase Ib, GDC-0810 will be given continuously beginning on Cycle 1 Day 1 in 28-day cycles. During Cycle 1 of the dose escalation, patients will return to the clinic on a weekly basis (Days 8, 15, and 22) for safety evaluation and collection of predose PK samples. On those days, treatment will be administered in the clinic. Study treatments, palbociclib will be given on Days 1–21 of each cycle and LHRH agonist will be given on Day 1 of each cycle. Evening dosing *(within 30 minutes after dinner or within 30 minutes of the consistently largest meal of the day)* may be initiated to alleviate gastrointestinal symptoms from GDC-0810. However, on Day 28 of Cycles 1, 2, and 3, the dose of GDC-0810 should be taken in the morning to allow trough PK sample collections on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1.

Similarly, on Day 1 of every subsequent new cycle of dosing beginning with Cycle 2, study treatment will be administered in the clinic following all the assessments as indicated in the Schedule of Activities.

All other doses of GDC-0810 or palbociclib will be administered on an outpatient basis. It is anticipated that some patients may occasionally forget to take a dose of GDC-0810 or palbociclib. In those cases, patients should just take the next scheduled dose, without compensating for the missed dose.

Palbociclib and GDC-0810 do not have to be taken together; however, each drug should be taken at a consistent time each day.

10.4 DOSE MODIFICATIONS

Patients who have had treatment interruptions due to reasons other than DLTs may restart daily dosing at the same dose at the discretion of the investigator when the toxicity has resolved to Grade ≤ 1 or baseline; however, any patients whose treatment is interrupted for an adverse event that is related to study drug and who do not restart treatment within 28 days will be withdrawn from study treatment.

For patients experiencing a DLT, treatment should be held until the severity of the toxicity decreases to Grade ≤ 1 or baseline. If they are deriving clinical benefit, patients may be restarted on study drug at the next lower dose level that has been tested in a previous cohort, at the discretion of the investigator and in consultation with the Sponsor. For Phase Ia and Phase IIa, no more than 2 dose reductions of GDC-0810 will be allowed.

For Phase Ib Cohort C1 a maximum of two dose reductions of GDC-0810 and palbociclib will be allowed. No dose reductions are planned for the LHRH agonists (Cohort D1). GDC-0810 dose reductions should be managed without changing regimen, for example, patients in Phase Ia who were being treated on a BID regimen will dose reduce to the next lower GDC-0810 dose level but still administered as BID. Similarly, Phase Ia patients who were being treated without a fasting requirement will dose reduce to the next lower dose level but still administered without a fasting requirement.

Doses reduced for drug-related toxicity should generally not be re-escalated. However, intrapatient re-escalation back to the previous dose level may be permitted at the discretion of the investigator and in consultation with the Sponsor.

10.4.1 Dose Modifications for Phase Ia, Ib Cohort D, and IIa

During the Phase Ia dose escalation DLT evaluation period, dose modifications will not be permitted; however, dose interruptions can be instituted for patient safety purposes. In Cycle 1, any interruption >7 days due to an adverse event assessed as related to GDC-0810 will meet the criteria for DLT.

After the DLT evaluation period is concluded and/or during the Phase IIa portion of the study, dose interruptions and/or reductions to the next lower dose level will be permitted as needed, provided that study discontinuation criteria have not been met (e.g., documented disease progression or unacceptable toxicity).

In Cohort D, no dose modification of the LHRH agonist will be permitted. However, the dose of GDC-0810 may be reduced in Cohort D1 or D2 on the basis of joint review by Sponsor and study investigators of available safety and tolerability data observed during the DLT assessment window.

GDC-0810 $must$ be held in the presence of the following toxicities potentially attributed to the study drug:

- Decrease in post-treatment glomerular filtration rate (GFR) of more than 25% as compared to baseline
- Any other Grade ≥ 3 adverse events potentially attributed to the study drug

GDC-0810 dose reductions may occur in increments of 200 mg. Therefore, the possible GDC-0810 doses permitted in Phase IIa are 600 mg, 400 mg, and 200 mg. Because no more than two dose reductions are permitted, patients should discontinue GDC-0810 if they experience adverse events at 200 mg of GDC-0810 requiring dose reduction.

Adverse events should be managed as shown in Table 4.

Table 4 Dose Modification and Management Guidelines

Toxicity	Dose Modification and Management Guidelines
Gastrointestinal Toxicities:	
General	• *Patients should be closely monitored for gastrointestinal (GI) symptoms and their effects on their wellbeing. Patients experiencing nausea, vomiting, and diarrhea should be treated and managed per standard of care and per protocol guidelines, including use of anti-diarrheal agents and appropriate supportive care including hydration and dietary modification if clinically indicated.* • *Remind patients to take GDC-0810 30 minutes after the largest meal of the day (preferably the evening).*
Diarrhea:	
General	*At first report of any grade diarrhea:* • *Initiate loperamide 4 mg, followed by 2 mg after each unformed stool. Daily dose should not exceed local recommendations in any 24-hour period.* • Infectious or alternate etiology should be excluded. • Grade ≥2 diarrhea is identified as an AESI requiring expedited reporting from study sites regardless of seriousness.
Grade 1	• Manage with *adequate* anti-diarrheal agents (e.g., loperamide) and *maximum* supportive care according to local standards and practices. • *Closely monitor for resolution.* • *If diarrhea does not resolve after 14 consecutive days, hold GDC-0810 until complete resolution of diarrhea.* • *Upon resolution, if Grade 1 diarrhea had persisted for > 1 week with no alternate etiology, consider starting loperamide 2 mg 1–2 times daily as secondary prophylaxis (i.e., use of loperamide to prevent further diarrhea).*

AESI = adverse event of special interest

Table 4 Dose Modification and Management Guidelines (cont.)

Toxicity	Dose Modification and Management Guidelines
Diarrhea (cont.):	
Grade 2	• *Manage with adequate anti-diarrheal agents (e.g., loperamide) and maximum supportive care according to local standards and practices.* • *Closely monitor for resolution.* • *H*old treatment with GDC-0810 until resolution to ≤ Grade 1. • *If Grade 2 diarrhea is recurrent after improvement to Grade 1, despite maximum medical management, reduce GDC-0810 by one dose level.* • *Upon resolution, if Grade 2 diarrhea is recurrent with no alternate etiology, consider starting loperamide 2 mg 1–2 times daily as secondary prophylaxis (i.e. use of loperamide to prevent further diarrhea).*
Grade ≥ 3	• *Manage with adequate anti-diarrheal agents (e.g., loperamide) and maximum supportive care according to local standards and practices.* • •*Closely monitor for resolution.* • Hold treatment with GDC-0810 until resolution to ≤ Grade 1. • At resolution of first occurrence, *reduce* the dose of GDC-0810 by one dose level *on improvement to Grade ≤1.* • *At resolution of* second occurrence, reduce dose of GDC-0810 by one dose level *on improvement to Grade ≤1.* • *On third occurrence, discontinue GDC-0810.* • *At any occurrence of Grade 4 diarrhea, consider discontinuation of GDC-0810.* • *Upon resolution, consider starting loperamide 2 mg 1–2 times daily as secondary prophylaxis (i.e., use of loperamide to prevent further diarrhea).*

AESI = adverse event of special interest

Table 4 Dose Modification and Management Guidelines (cont.)

Toxicity	Dose Modification and Management Guidelines
Nausea and/or Vomiting:	
General	• Grade ≥2 vomiting and Grade ≥3 nausea are identified as AESIs requiring expedited reporting from study sites regardless of seriousness.
Grade 1–2	• Manage with anti-emetics and supportive care according to local standards and practices. If persistent despite maximal medical therapy, hold treatment with GDC-0810 until resolution to Grade ≤1.
Grade ≥3	• Manage with anti-emetics and supportive care. • Hold treatment with GDC-0810 until resolution to Grade ≤1. • Reduce GDC-0810 dose by one dose level when treatment resumes.
Venous Thromboembolic Events (including Pulmonary Embolism):	
General	• Patients should be advised to seek immediate medical attention if they become aware of any symptoms of pulmonary embolism (PE) or deep vein thrombosis (DVT), such as acute onset of chest pain, shortness of breath, or swelling in extremities. • Grade ≥2 VTEs are identified as AESIs requiring expedited reporting from study sites regardless of seriousness.
Grade 1–2	• Manage and treat patients according to institutional guidelines and local standards of care. • May consider anti-coagulation and/or inferior vena cava (IVC) filter based upon local best standards and practices after an individual assessment of risk benefit for each patient.
Grade ≥3	• As Grade 1–2. • Hold dosing with GDC-0810 until the patient is stable. • Discuss with study Medical Monitor for appropriate dose modification and management.

AESI = adverse event of special interest

Table 4 Dose Modification and Management Guidelines (cont.)

Toxicity	Dose Modification and Management Guidelines
Vaginal or Uterine Hemorrhage:	
General	• Grade ≥2 vaginal or uterine hemorrhage is identified as an AESI requiring expedited reporting from study sites regardless of seriousness. • Prior to enrollment, screening scan of the uterus with transvaginal ultrasound must be performed. Due to the potential risks of changes in the female reproductive tract and uterotrophic effects, patients with a history of endometrial polyps, endometrial cancer, atypical endometrial hyperplasia, or other significant endometrial disorders should be excluded unless they have undergone total hysterectomy, and there is no evidence of active disease.
Grade 1	• Seek consultation with gynecologist or other specialist for differential diagnosis and appropriate management. • Transvaginal ultrasound should be considered.
Grade ≥2	• As Grade 1. • Hold dosing with GDC-0810 until resolution to Grade ≤1. • Discuss with study Medical Monitor for appropriate dose modification and management
Elevation of hepatic transaminases:	
General	• *Patients presenting with jaundice, coagulopathy, abdominal pain, or other symptoms suggestive of hepatic pathology should have their liver function tests checked and imaging of the liver performed. If the liver enzymes are elevated with no obvious malignant cause found, a hepatologist should be consulted.* • *Patients experiencing hepatic enzyme elevation should be treated and managed per standard of care.*
Grade ≥3	• *Hold study drug until resolution to baseline or below upper limit of normal (ULN).*
AESI = adverse event of special interest.	

10.4.2 Dose Modifications for Phase Ib Cohort C1

During the dose escalation DLT evaluation period, dose modifications will not be permitted; however, dose interruptions can be instituted for patient safety purposes. In Phase Ib Cohort C1, any grade non-hematologic toxicity assessed as related to GDC-0810 and/or palbociclib that leads to study drug interruption of >7 days' duration will meet the criteria for DLT. Patients who miss ≥ 7 doses of GDC-0810 or ≥ 5 doses of palbociclib during the DLT evaluation period due to reasons other than a DLT will be replaced.

After the DLT evaluation period is concluded, dose interruptions and/or reductions to the next lower dose level will be permitted as needed, provided that study discontinuation criteria have not been met (e.g., documented disease progression or unacceptable toxicity). Dose modification guidelines for treatment-related non-hematologic and hematologic toxicities are shown in Table 5 and Table 6, respectively.

GDC-0810 dose reductions may occur in decrements of 200 mg. Therefore, the possible GDC-0810 doses permitted in Phase Ib Cohorts C1 and C2 are 600 mg, 400 mg, and 200 mg. Because no more than two dose reductions are permitted, patients should discontinue GDC-0810 if they experience adverse events at 200 mg of GDC-0810 requiring dose reduction.

Palbociclib dose reductions may occur in decrements of 25 mg. Therefore, the possible palbociclib doses permitted in Phase Ib Cohorts C1, C2 and C3 are 125 mg, 100 mg, and 75 mg. Palbociclib dose de-escalation below 75 mg/day is not allowed, but in consultation with the sponsor, the schedule may be changed for example to 75 mg/day 2 weeks on followed by 2 weeks off (2/2 schedule).

Both GDC-0810 and palbociclib $must$ be held in the presence of the following toxicities potentially attributed to the study drug:

- Decrease in post-treatment GFR of more than 25% as compared to baseline
- Any other Grade ≥ 3 non-hematologic adverse events potentially attributed to the study drug.

Table 5 Dose Modification Guidelines for Treatment-Related Non-Hematologic Toxicities

Toxicity	Palbociclib and/or GDC-0810 Dose Modification
Gastrointestinal Toxicities:	
General	• *Patients should be closely monitored for gastrointestinal (GI) symptoms and their effects on their wellbeing. Patients experiencing nausea, vomiting, and diarrhea should be treated and managed per standard of care and per protocol guidelines, including use of anti-diarrheal agents and appropriate supportive care including hydration and dietary modification if clinically indicated.*
Diarrhea:	
General and Grade 1	• See Section 10.4.1. • *If diarrhea does not resolve after 14 days and GDC-0810 has already been held, consider withholding palbociclib.* • *If palbociclib hold was required, consider starting loperamide 2 mg 1–2 times daily as secondary prophylaxis (i.e., use of loperamide to prevent further diarrhea).*
Grade 2 diarrhea	• *See Section* 10.4.1. • If *diarrhea persists for more than 7 days after GDC-0810 is held,* consider withholding palbociclib until symptoms resolve to Grade ≤1. • *If palbociclib hold was required, consider starting loperamide 2 mg 1–2 times daily as secondary prophylaxis (i.e., use of loperamide to prevent further diarrhea) upon restart.*
Grade ≥3 diarrhea	• *Manage with adequate anti-diarrheal agents (e.g., loperamide) and maximum supportive care according to local standards and practices.* • *Closely monitor for resolution.* • Withhold GDC-0810 and palbociclib until symptoms resolve to Grade ≤1. • At resolution of first occurrence, *reduce* the dose of GDC-0810 *by one dose level on improvement to Grade ≤1. Consider reducing* palbociclib by one dose level. • At resolution of second occurrence, reduce dose of GDC-0810 by one dose level *on improvement to Grade ≤1.* Consider reducing palbociclib by one dose level. • *On third occurrence, discontinue GDC-0810* • *At any occurrence of Grade 4 diarrhea, consider discontinuation of GDC-0810.* • *Upon resolution, consider starting loperamide 2 mg 1–2 times daily as secondary prophylaxis (i.e., use of loperamide to prevent further diarrhea).*

Table 5 Dose Modification Guidelines for Treatment-Related Non-Hematologic Toxicities (cont.)

Toxicity	Palbociclib and/or GDC-0810 Dose Modification
Nausea and or Vomiting:	
General and Grade 1	See Section 10.4.1.
Grade ≥2 nausea or vomiting	• If persistent despite maximal medical therapy, withhold GDC-0810 until recovery to Grade ≤1. *If no improvement is noted in palbociclib combination patient, consider additionally withholding palbociclib until recovery to Grade ≤1.*
Grade ≥3 nausea or vomiting	• Manage with anti-emetics and supportive care. • Withhold GDC-0810 and/or palbociclib until symptoms resolve to Grade ≤1. • On resolution of first occurrence, reduce dose of GDC-0810 by one dose level when treatment resumes and consider reducing dose of palbociclib. • On resolution of second occurrence, reduce dose of GDC-0810 and/or palbociclib by one dose level when treatment resumes.
Venous thromboembolic events (including pulmonary embolism):	
General and Grade 1–2	See Section 10.4.1.
Grade ≥3 venous thromboembolic events (including pulmonary embolism)	• Withhold GDC-0810 and palbociclib until patient is stable and consult with Sponsor before resuming treatment.
Vaginal hemorrhage:	
General and Grade 1	See Section 10.4.1.
Grade ≥2 vaginal hemorrhage	• Withhold GDC-0810 and palbociclib until Grade ≤1 and consult with Sponsor before resuming treatment.
Grade ≥3 non-hematologic toxicity	• Withhold GDC-0810 and/or palbociclib until symptoms resolve to Grade ≤1 or Grade ≤2 (after discussion with Medical Monitor). • If repeated toxicity is seen in the next cycle or if recovery from Grade 3 is delayed beyond 7 days discuss with Medical Monitor.

Table 5 Dose Modification Guidelines for Treatment-Related Non-Hematologic Toxicities (cont.)

Toxicity	Palbociclib and/or GDC-0810 Dose Modification
Elevation of hepatic transaminases:	
General	• *Patients presenting with jaundice, coagulopathy, abdominal pain, or other symptoms suggestive of hepatic pathology should have their liver function tests checked and imaging of the liver performed. If the liver enzymes are elevated with no obvious malignant cause found, a hepatologist should be consulted.* • *Patients experiencing hepatic enzyme elevation should be treated and managed per standard of care.*
Grade ≥3	• *Hold study drug until resolution to baseline or below upper limit of normal (ULN).*

Table 6 Dose Modification Guidelines for Hematologic Toxicities

Toxicity	Palbociclib	GDC-0810
Neutropenia or thrombocytopenia Grade ≤ 2	No dose modification required.	No dose modification required.
Uncomplicated Grade 3 neutropenia	Withhold palbociclib until recovery to Grade ≤ 2 ($\geq 1000/mm^3$). No dose adjustment is required unless recovery of neutrophil count is delayed[a,b], in which case reduce by one dose level.	No dose modification required.
Uncomplicated Grade 4 neutropenia (ANC $< 500/mm^3$)	Withhold palbociclib until recovery to Grade ≤ 2 ($\geq 1000/mm^3$). Resume at next lower dose. Reduce by two dose levels[c] if neutrophil recovery is delayed[a] or in case of recurrent Grade 4 event.	No dose modification required.
Grade ≥ 3 neutropenia associated with infection or fever	Withhold palbociclib until neutrophil count recovery to Grade ≤ 2 ($\geq 1000/mm^3$) and afebrile and infection is clinically improving. Resume palbociclib at next lower dose. Reduce by two dose levels[c] if neutrophil recovery is delayed[a]. In case of Grade 4 febrile neutropenia, discuss with Medical Monitor prior to resuming palbociclib.	No dose modification required.
Uncomplicated Grade ≥ 3 thrombocytopenia (platelet count $< 50,000/mm^3$)	Withhold palbociclib until recovery to Grade ≤ 2 ($\geq 50,000/mm^3$). Resume at next lower dose. Reduce by two dose levels[c] if platelet count recovery is delayed[a] or in case of recurrent Grade 4 event.	No dose modification required.

ANC = absolute neutrophil count.

[a] If recovery of neutrophils to $\geq 1000/mm^3$ or platelet count to $\geq 50,000/mm^3$ takes > 2 weeks (including dose holding due to toxicity, the scheduled week off treatment, or > 7 days of cycle delay).

[b] If uncomplicated Grade 3 neutropenia recurs in 2 consecutive cycles, after recovery as per retreatment criteria (ANC $\geq 1000/mm^3$ and no fever), treatment may restart at the next lower dose level at investigator's discretion.

[c] If no further dose reduction is possible (i.e, patient is already receiving 75 mg/day according to the 3/1 schedule), consider changing the schedule to 75 mg/day, 2 weeks on/2 weeks off, or discontinue palbociclib and continue with GDC-0810 alone.

Table 6 Dose Modification Guidelines for Hematologic Toxicities (cont.)

Toxicity	Palbociclib	GDC-0810
Grade ≥3 thrombocytopenia (platelet count<50,000/mm^3) associated with bleeding	Withhold palbociclib until platelet count recovery to Grade ≤2 (≥50,000/mm^3) and clinically stable. Resume palbociclib at next lower dose. Reduce by two dose levels[c] if platelet count recovery is delayed[a]. In case of recurrent Grade 3 event following a previous delayed recovery of platelet count, discuss with Medical Monitor. In case of Grade 4 thrombocytopenia associated with bleeding, discuss with Medical Monitor prior to resuming palbociclib.	No dose modification required.
Grade 3 anaemia	*Withhold palbociclib until recovery to Grade ≤2 (≥8.0 g/dL). No dose adjustment is required unless recovery of hemoglobin is delayed [a], in which case reduce by one dose level.*	*No dose modification required.*
Grade 4 anaemia	*Withhold palbociclib until recovery to Grade ≤2 (≥8.0 g/dL). Resume at next lower dose. Reduce by two dose levels [c] if hemoglobin recovery is delayed [a] or in case of recurrent Grade 4 event.*	*No dose modification required.*

ANC = absolute neutrophil count.

[a] If recovery of neutrophils to ≥1000/mm^3 or , platelet count to ≥50,000/mm^3*, or hemoglobin to ≥8.0 g/dL* takes >2 weeks (including dose holding due to toxicity, the scheduled week off treatment, or >7 days of cycle delay).

[b] If uncomplicated Grade 3 neutropenia recurs in 2 consecutive cycles, after recovery as per retreatment criteria (ANC≥1000/mm^3 and no fever), treatment may restart at the next lower dose level at investigator's discretion.

[c] If no further dose reduction is possible (i.e, patient is already receiving 75 mg/day according to the 3/1 schedule), consider changing the schedule to 75 mg/day, 2 weeks on/2 weeks off, or discontinue palbociclib and continue with GDC-0810 alone.

10.4.3 Concomitant Medications and Treatments

Concomitant therapy includes any medications *(prescription drugs* or over-the-counter *drugs, herbal or homeopathic remedies, nutritional supplements)* used by a patient from 7 days before screening through the study completion visit.

All concomitant medications administered to the patient will be reported from 7 days before screening through 4 weeks following receipt of the last dose of study drug. The drug name, its route of administration, as well as its start and stop dates will be recorded.

Any new anti-cancer therapies initiated within the safety follow-up visit (including drug name and date of initiation) will be recorded as well.

Use of Colony Stimulating Factors

Primary prophylactic use of colony stimulating factors (CSF) is not permitted, but they may be used to treat treatment-emergent neutropenia as per current American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2006). If neutropenic complications are observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator but only if dose reduction or delay are not considered a reasonable alternative.

10.4.3.1 Drug Interactions of GDC-0810

Nonclinical studies have shown that the major metabolic pathway of GDC-0810 was via glucuronidation by multiple UDP-glucuronosyltransferase (UGT) isoforms. GDC-0810 was shown to inhibit human CYP enzymes in vitro, especially CYP2B6 and CYP2C enzymes; therefore, drug-drug interactions with co-administered CYP2B6 and CYP2C substrates cannot be excluded and should be avoided. Note that many of these medications are metabolized by multiple CYP enzymes, thus attenuating the potential for drug-drug interactions to some extent. If there is clinical need for a particular CYP2B6 and CYP2C substrate drug, dose adjustments and/or use of alternative medications are recommended. A list of sensitive in vivo CYP2B6 and CYP2C substrates and substrates with narrow therapeutic range can be found in Appendix 8a. GDC-0810 was also shown to inhibit human transporters in vitro, including OATP1B1/1B3. A drug-drug interaction study with pravastatin as the OATP1B1/1B3 substrate has been initiated to evaluate the potential risk. *The preliminary PK results showed no significant drug-drug interaction between GDC-0810 and pravastatin.*

10.4.3.2 Drug Interactions of Palbociclib

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A.

10.4.3.3 Agents that may increase palbociclib plasma concentrations

Effect of CYP3A inhibitors

Co-administration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%. Avoid concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole). Avoid grapefruit or grapefruit juice during palbociclib treatment (Ibrance® Prescribing Information). If co-administration of palbociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of palbociclib. A list of strong CYP3A inhibitors can be found in Appendix 8b.

10.4.3.4 Agents that may decrease palbociclib plasma concentrations

Effect of CYP3A inducers

Co-administration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85% (Ibrance® Prescribing Information). Avoid concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine and St. John's Wort). Co-administration of moderate CYP3A inducers may also decrease the plasma exposure of palbociclib. Avoid concomitant use of moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin). A list of strong and moderate CYP3A inducers can be found in Appendix 8c.

10.4.3.5 Drugs that may have their plasma concentrations altered by palbociclib

Co-administration of midazolam with multiple doses of palbociclib increased the midazolam plasma exposure by 61%, in healthy subjects, compared with administration of midazolam alone. The dose of the sensitive CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced as may increase their exposure (Ibrance® Prescribing Information). A list of sensitive in vivo CYP3A substrates and CYP3A substrates with narrow therapeutic range can be found in Appendix 8a.

10.4.3.6 Drug Interactions of LHRH Agonists

Leuprolide acetate

No pharmacokinetic-based drug-drug interaction studies have been conducted; however, drug interactions are not expected to occur.

Goserelin acetate

No formal drug-drug interaction studies have been performed. No confirmed interactions have been reported between goserelin acetate (Zoladex®) and other drugs.

Triptorelin pamoate

No drug-drug interaction studies involving triptorelin have been conducted.

Drug-Drug Interactions with GDC-0810 and Palbociclib

Glucuronidation is the major metabolic pathway of GDC-0810. GDC-0810 is a weak inhibitor of CYP3A. Palbociclib is primarily metabolized by CYP3A and SULT2A1 and shown as a weak time-dependent inhibitor of CYP3A. In general, on the basis of data on GDC-0810 and palbociclib, the risk for drug interactions is low.

Drug-Drug Interactions with GDC-0810 and LHRH Agonists

No pharmacokinetic-based drug-drug interaction studies have been conducted with LHRH agonists. However, because LHRH agonists are peptides that are primarily degraded by peptidase and not by cytochrome P-450 enzymes and glucuronidation, the risk for drug interactions is low.

Prohibited Therapies

No other hormonal therapy, chemotherapy, immunotherapy, or experimental anti-cancer medications will be permitted while the patient is in the study.

Other Therapies

Symptomatic anti-emetics, anti-diarrheal therapy, as well as other palliative and supportive care for disease- or treatment-related symptoms may be administered at the investigator's discretion. All concomitant medication and/or therapies should be documented in the patient's CRF. In certain instances, focal radiation therapy for palliation of bone disease-related symptoms might be allowable after discussion with the Sponsor; however, the need for radiation therapy will generally be considered indicative of progressive disease. Bone-sparing agents (e.g., bisphosphonates, denosumab) for palliation of bone metastases or for the treatment of osteoporosis/osteopenia are allowed in the study. In general, it is recommended to stop GDC-0810 and/or palbociclib treatment at least 7 days prior to surgical procedures. Postoperatively, the decision to reinitiate GDC-0810 and/or palbociclib treatment should be based upon a clinical assessment of satisfactory wound healing and recovery from surgery.

Lifestyle Guidelines

Patients should take precautionary measures regarding sun exposure, with daily sunscreen use and wearing protective clothing, sunglasses, and hats when outdoors.

Dietary Restrictions

Patients enrolled in Cohort C1 who are receiving GDC-0810 concurrently with palbociclib should avoid grapefruit and grapefruit juice due to the CYP3A inhibition.

10.5 STUDY DRUG ACCOUNTABILITY

The Sponsor (or designee) will ship GDC-0810 to the investigational sites. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Study drug treatments, palbociclib and LHRH agonist will be prescribed by the study sites and cost of study treatment will be reimbursed by the Sponsor.

An accurate and current accounting of the dispensing and return of all applicable study drug (i.e. GDC-0810 and study drug treatment) for each patient will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the patient will be recorded on the accountability log. The study monitor will verify these documents throughout the course of the study.

At the end of the study, the Sponsor will provide instructions as to the disposition of any unused study drug. If destruction at the site is authorized, the investigator must ensure that all investigational product is destroyed in compliance with the applicable environmental regulations, institutional policy, and any other special instructions provided by the Sponsor. Drug destruction must be adequately documented.

Post-Trial Access to GDC-0810

The Sponsor (Genentech) is a member of the Roche group and is subject to Roche's global policies. The Sponsor will offer post-trial access to the study drug GDC-0810 free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below. A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- *The* data suggest that the study drug is not effective for postmenopausal women with ER+ advanced breast cancer.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for postmenopausal women with ER+ advanced breast cancer.
- Provision of study drug is not permitted under the laws and regulations of the patient's country.

Genentech does not intend to provide other study interventions to patients after the conclusion of the study or any earlier withdrawal.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

10.6 MEASURES OF TREATMENT COMPLIANCE

At each clinic visit starting with Cycle 2, patients will be asked to return any remaining applicable study drug GDC-0810 and/or study drug treatment (i.e. palbociclib) from the previous dosing cycle as well as all used and unused study drug containers.

In the dose escalation portion of the study, patients should also bring their study drug containers to the weekly visits in Cycle 1 in order to verify treatment compliance for the DLT evaluation period.

Treatment compliance will be defined as the number of tablets or capsules taken divided by the expected number of tablets and reported as percentage. In case of dose reductions, the expected number of tablets or capsules should reflect the new dose level.

Tablets or capsules that are not returned will be considered to have been taken, unless otherwise specified in the patient's CRF.

11. STUDY PROCEDURES AND GUIDELINES

Schedule of Activities representing the required testing procedures to be performed during the study are diagrammed in Appendix 1 (Phase Ia), Appendix 2 (Phase IIa), Appendix 3 (Phase Ib Cohort C1), and Appendix 4 (Phase Ib Cohort D1).

Prior to conducting any study-related activities, written informed consent and any other authorizations must be signed and dated by the patient.

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In those cases, the investigator should take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The Sponsor study team should be informed of these incidents in a timely fashion.

11.1 CLINICAL ASSESSMENTS

11.1.1 Demographics

Demographic information (e.g., date of birth and race) will be recorded at screening.

11.1.2 Medical History

Relevant medical history includes clinically significant diseases; smoking history, use of alcohol and drugs of abuse, history of current disease, surgeries, other pertinent clinical conditions, and information regarding underlying diseases will be recorded at screening.

All medications used by the patient within 7 days before the screening visit (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) will be recorded at screening.

11.1.3 Physical Examination

A complete physical examination will be performed by either the investigator or a sub-investigator at screening. Qualified staff (e.g., nurses or physician assistants) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and followed by a physician or other qualified staff at the next scheduled visit.

The physical examination should include, but is not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system, as well as examination of known and suspected sites of disease. Height will be recorded at screening only.

11.1.4 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed at screening and at every clinic visit.

11.1.5 Performance Status

The ECOG performance status scale will be assessed at screening and at every clinic visit (Appendix 6).

11.1.6 Adverse Events

Assessment of adverse events will include type, incidence, severity (graded by the NCI CTCAE, Version 4.0, Appendix 7), timing, seriousness, and relatedness. Adverse events will be assessed at every clinic visit.

11.1.7 Concomitant Medications and Treatments

All concomitant medication and concurrent therapies will be documented at screening and at every clinic visit. The indication for administration and dates of medication will be captured.

11.1.8 Tumor Assessments

Disease assessments will be performed at screening*, per institutional guidelines, and as clinically indicated.*

Imaging studies will include a CT scan of the chest, abdomen, and pelvis, plus a bone scan. At screening, a CT/MRI brain should be obtained if clinically indicated to rule out newly diagnosed, untreated brain metastasis.

Radiographic confirmation of objective tumor response or disease progression will be based on RECIST v1.1 (Eisenhauer et al. 2009).

The same method of assessment and the same technique should be used at screening and during follow up. Intravenous (IV) contrast is required when not medically contraindicated. Patients who have a contraindication to IV contrast may have MRI exams of the abdomen and pelvis performed in lieu of CTs and a non-contrast CT of the chest. Tumor evaluation by PET scan or by ultrasound may not substitute for CT or MRI scans. However, a CT for tumor assessment may be acquired on a PET/CT scanner if it is of full diagnostic quality and includes IV contrast.

11.1.9 Endometrial Thickness Assessments (if applicable)

To assess for any potential effect of *study treatment* on the uterus, transvaginal ultrasound scans will be performed to monitor endometrial thickness *at screening, the study drug discontinuation visit*, and as clinically indicated. Transvaginal ultrasounds are not required for patients who have had a hysterectomy.

11.2 CLINICAL LABORATORY MEASUREMENTS

Blood and urine will be obtained *as clinically indicated (except creatinine and liver function tests)* and analyzed at a local or central laboratory for hematology, blood chemistry profile, and urinalysis, respectively. *Liver function test and creatinine will be collected at least monthly and as clinically indicated.* Appendix 5 lists all of the specific tests that will be performed.

Investigators may have additional local laboratory tests performed for the purpose of planning treatment administration, dose modification, or following adverse events.

11.3 ELECTROCARDIOGRAM (ECG)

11.3.1 Phase Ia

Standard single 12-lead ECGs (with a 10-second rhythm strip) will be collected at screening and at Cycle 2 Day 1 at the 2-hour post-dose timepoint (prior to the respective PK sample collection). ECGs should be collected after the patient has rested quietly and is awake in a fully supine (or semi-recumbent, if supine is not tolerated) position for 5 to 10 minutes and prior to any blood draw collection.

11.3.2 Phase IIa

During Phase IIa, all patients will participate in the evaluation of the effect of GDC-0810 on ventricular repolarization. Triplicate 12-lead ECGs (with a 10-second rhythm strip) will be collected approximately 2 minutes apart at screening, at Cycle *2* Day 1 predose, and at 1, *2,* 3, *4,* and 6 hours following dosing.

After each set of ECGs on Cycle 2 Day 1, blood samples to assess PK will be collected (see Section 11.4.2).

ECGs will be recorded and evaluated at the clinical study (local) site for the purposes of real-time cardiac safety monitoring for individual patients and will be subsequently

analyzed at a designated central facility for the purposes of assessing the effects of GDC-0810 on the QTc and other cardiac intervals. For real-time safety monitoring of patients, only one ECG printout per timepoint (of the triplicate samples) will need to be reviewed by the investigator. For the purposes of central analysis, triplicate ECGs will be obtained in a rigorous and standardized fashion and transmitted digitally to the central reading facility for review and interpretation by specialized cardiac readers.

11.3.3 Phase Ib

Standard single 12-lead ECGs (with a 10-second rhythm strip) will be collected at screening, Cycle 1 Day 1 (prior to first dose), Cycle 2 Day 1 (prior to the respective PK sample collection), and at the end of treatment. ECGs should be collected after the patient has rested quietly and is awake in a fully supine (or semi-recumbent, if supine is not tolerated) position for 5 to 10 minutes and prior to any blood draw collection.

11.4 PHARMACOKINETIC MEASUREMENTS

11.4.1 Phase Ia

Blood samples for full PK profile analysis of GDC-0810 (and its acyl-glucuronide and N-glucuronide metabolites) will be collected on Day –7 at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 (Day –6), and 48 (Day –5) hours postdose. A second set will be collected on Day 29 (Cycle 2 Day 1) at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours postdose (Cycle 2 Day 2, prior to the next dose).

11.4.2 Phase IIa

Blood samples for determining trough PK (predose) concentrations of GDC-0810 will be collected in Cycles *1,* 2, 3 and 4.

Additionally, on Cycle 2 Day 1, PK samples will also be collected predose and at 1, 2, 3, 4, 6 hours following dosing. If PK sampling times coincide with ECG collection times, the ECGs have to be assessed prior to PK blood collection.

11.4.3 Phase Ib

For Cohort C1, on Cycle 1 Day 1 and Cycle 1 Day 8, PK samples will be collected predose and at 1, 2, 3, 4, and 6 hours following dosing to measure the concentrations of GDC-0810 and palbociclib. Additionally, blood samples for determining trough PK (predose) concentrations of GDC-0810 and palbociclib will be collected on Day 1 in Cycles 2, 3, *4,* and *at end of treatment*.

For Cohort D1, on Cycle 1 Day 1 and Cycle 2 Day 1, PK samples will be collected predose and at 1, 2, 3, 4, and 6 hours following dosing to measure the concentrations of GDC-0810 and LHRH agonists. If PK sampling times coincide with ECG collection times, the ECGs have to be assessed prior to PK blood collection. Additionally, blood samples for determining trough PK (pre-dose) concentrations of GDC-0810 and LHRH agonists will be collected on Day 1 in Cycles 3, *4,* and *at end of treatment*.

See the Laboratory Manual for collection and processing procedures.

11.5 CORRELATIVE STUDIES

11.5.1 FES-PET

Imaging with FES-PET will be performed to quantify ER expression in the tumor and to assess for PD response to GDC-0810 therapy. While FES uptake can vary between patients, in general, the FES uptake is fairly consistent across lesions at a given timepoint, and the average uptake provides a reasonable summary of ER expression for an individual patient (Kurland et al. 2011). Factors that can affect standardized uptake value, such as sex hormone-binding globulin (SHBG), will be adjusted as per standard protocol (Peterson et al. 2011). In addition, a washout period for patients previously treated with tamoxifen (at least 2 months), fulvestrant (at least 6 months), or other hormonal therapy (at least 2 weeks) will be required due to the long half-life of each drug and its potential to interfere with FES uptake. FES-PET studies will be performed as hybrid PET/CT imaging for attenuation correction and lesion localization. FES-PET scan is not required for patients enrolled in Phase Ib.

11.5.1.1 Phase Ia

During dose escalation, pre- and post-treatment functional ER imaging with FES-PET/CT scans will be performed starting at dose level 2 (200 mg) at screening (baseline) and at 4 weeks of treatment (Cycle 2 Day 3), as per Table 7:

Table 7 Pre- and Post-Treatment Functional ER Imaging with FES-PET/CT Schedule (Phase Ia)

Cycle 2 Day 1	PK sampling day at 0 (predose) to 8 hours postdose as per protocol Section 11.4.1
Cycle 2 Day 2	No GDC-0810 dose prior to clinic visit 24-hr PK sample **Take GDC-0810 dose in the evening that day (please see below instructions for fasting before and after)**
Cycle 2 Day 3	**FES-PET scan during the period between ≥18 and ≤24 hours post the evening dose on C2D2** **No GDC-0810 dose on this day**
Cycle 2 Day 4	Resume daily dosing of GDC-0810 in the morning as per protocol Section 10.3.1
Cycle 2 Day 8 (± 1 day)	Optional biopsy as per protocol Section 11.5.2.1 below
Cycle 3 (~same day as CT/MRI scans)	FES-PET scan during the period between ≥2 and ≤12 hours post the morning dose ***Only necessary if Cycle 2 Day 3 scan shows incomplete pharmacodynamic activity of GDC-0810***

For more details:

Cycle 2 Day 2: After the 24-hour postdose PK sample is collected (Section 11.4.1), the patient will be instructed to take her next dose of GDC-0810 at home that evening at 6:00 p.m. ± 1 hour, observing a fasting period of at least 4 to 6 hours predose and 1 hour of fasting postdose, followed by dinner. For example, start fasting after *completion of* lunch at 12:00 noon, take the dose of GDC-0810 at 6:00 p.m., followed by dinner at 7:00 p.m.

Cycle 2 Day 3: Without taking another dose of GDC-0810 in the morning, the FES-PET/CT scan should be performed during the period between ≥18 and ≤24 hours after the evening dose administered on Cycle 2 Day 2. Following the same example above, the scan should be performed between 12:00 noon and 6:00 p.m. No dose of GDC-0810 will be administered on this day.

Cycle 2 Day 4: Resume daily dosing of GDC-0810 in the morning, after fasting overnight; food should not be eaten for at least 1 hour after taking GDC-0810.

Cycle 3: Only necessary if the Cycle 2 Day 3 scan shows incomplete PD activity of GDC-0810: a repeat FES-PET/CT scan will be performed on the same day as the Cycle 3 CT/MRI tumor evaluation scans during the period between ≥2 and ≤12 hours postdose (administered that morning at the normal time).

If low FES uptake is observed at baseline, the investigator will determine whether the post-treatment scans are warranted.

11.5.1.2 Phase IIa

During Phase IIa, pre- and post-treatment functional ER imaging with FES-PET/CT scans will be performed in all Cohort A1 patients at screening (baseline) and at Cycle 3, as per Table 8:

Table 8 Pre- and Post-Treatment Functional ER Imaging with FES-PET/CT Schedule (Phase IIa)

COHORT A1 ONLY	
Cycle 3 Day 1	Perform all routine labs as per protocol Section 11.2, including ECG assessments
Cycle 3 Day 2	Take GDC-0810 dose in the evening this day
Cycle 3 Day 3	No GDC-0810 dose on this day **Perform FES-PET scan during the period between ≥18 and ≤24 hours post the evening dose on C3D2**
Cycle 3 Day 4	Resume normal GDC-0810 dosing
Cycle 3 Day 8 (± 1 day)	Biopsy as per protocol Section 11.5.2.2 below (Patients in Cohort A2 can have the biopsy any time during Cycle 3)

In addition, if feasible, a FES-PET/CT scan should also be performed at the time when disease progression is suspected (especially if disease progression occurs prior to Cycle 3).

11.5.2 Tumor Biopsies

Pre- and post-treatment tumor biopsies from the same (whenever feasible) soft tissue or visceral metastatic lesion will be collected to evaluate the histology of the tumor versus stroma, to assess for ER degradation and PR protein levels (via IHC), PR downregulation, proliferative index (Ki67), and ER target gene modulation studies. Tumor biopsies will also be used for DNA and /or RNA extraction to enable next generation sequencing (NGS) *and/ or whole genome sequencing (WGS)* for exploratory research on biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways).

11.5.2.1 Phase Ia

Optional tumor biopsies will be collected predose and after 4 weeks of treatment (Cycle 2 Day 8 ± 1 day, during the period between ≥2 and ≤12 hours postdose). This schedule will allow the patient to have resumed daily morning dosing of GDC-0810 for at least 3 days since the FES-PET/CT scan was performed.

11.5.2.2 Phase IIa

All Cohort A patients with safely accessible soft tissue and/or visceral metastases will be required to have tumor biopsies. Optional tumor biopsies will be collected for Cohort B patients with safely accessible soft tissue and/or visceral metastases. Biopsies should be performed predose, at Cycle 3 (Day 8 *±1 day* for patients in Cohort A1), and if feasible, at the time when disease progression is suspected (especially if disease progression occurs prior to Cycle 3). Biopsies should be collected during the period between ≥2 and ≤12 hours postdose.

11.5.2.3 Phase Ib

Tumor biopsies are mandatory for patients in Phase Ib with safely accessible soft tissue and/or visceral metastases. Biopsies should be obtained predose and after 2 weeks of treatment (Cycle 1 Day 15±1 day, during the period between ≥2 and ≤12 hours postdose) *and at the time of disease progression*.

11.5.2.4 Archival Tissue Collection

Archival paraffin-embedded tissue may be collected to evaluate the histology of the tumor in all Phases of this study (Ia, Ib, IIa) for DNA and /or RNA extraction to enable next generation sequencing (NGS) for exploratory research on non-inherited biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways). If fresh tumor tissue biopsy cannot be obtained at screening, every reasonable effort should be made to obtain the most recent archival tissue sample. Tumor blocks are preferred, but in the event that local regulations prevent the shipment of tumor blocks, 15–20 unstained, serially cut slides are requested. Minimum tissue requirements are further described in the laboratory manual. Cytological, fine-needle aspiration, and decalcified bone biopsy samples are not acceptable. Tissue blocks from archival biopsies will be returned to the archival facility from which they were originally received.

11.5.3 Circulating Tumor DNA Analyses

In Phase Ia and IIa, additional blood samples will be collected at screening and at the time of study discontinuation for analysis of circulating tumor DNA (ctDNA). During Phase IIa, ctDNA will also be collected at Cycle 3.

In Phase Ib, additional blood samples will be collected at screening, Cycle 3, Cycle 5, and at the time of study discontinuation for analysis of ctDNA.

Recent nonclinical and clinical data suggest that mutations in ER-α and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) are associated with endocrine resistant breast cancer. To gain insights into potential causal relationships between GDC-0810's clinical activity and resistance mechanisms, mutational status of both of these genes will be monitored in ctDNA isolated from plasma using next generation sequencing *and other molecular technologies*.

11.5.4 Pharmacogenomic (PGx) Evaluations

It is established that genetic variants of drug-metabolizing enzymes and transporters can affect the PK of drugs, affecting their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1, which facilitates the metabolism and excretion of SN-38 (the active metabolite of irinotecan), are at higher risk for adverse effects associated with the use of standard doses of irinotecan (O'Dwyer et al. 2006). Similarly, it has recently been shown that patients with genetic polymorphisms in the gene that encodes cytidine deaminase have decreased clearance of gemcitabine and an increased incidence of neutropenia when they received platinum containing drugs or fluorouracil concurrently (Sugiyama et al. 2007).

For potential PGx analysis of genes that may affect the PK and safety of GDC-0810, a mandatory blood sample for DNA isolation will be collected from all patients in Phase IIa and Ib portions of this study prior to the first dose of GDC-0810 on Cycle 1 Day 1.

12. SAFETY ASSESSMENTS

12.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 12.3.

12.1.1 Adverse Events

According to the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP), an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described Section 12.3
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

12.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 12.2.5.10)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 12.2.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 12.3 for reporting instructions).

12.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately, irrespective of severity or regulatory seriousness (i.e., no more than 24 hours after learning of the event; see Section 12.3 for reporting instructions). Adverse events of special interest for this study include the following:

General Drug Development Adverse Events

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 12.3)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Adverse Events of Interest

- DLTs occurring during the DLT assessment window
- Grade $\geq$2 vomiting/diarrhea

- Grade ≥3 nausea
- Grade ≥2 thromboembolic events (including pulmonary embolism)
- Grade ≥ 2 vaginal or uterine hemorrhage
- Grade ≥3 elevation of ALT or AST

Adverse Events of Special Interest for Patients *Assigned* to Receive GDC-0810 in Combination with Palbociclib

- Grade 4 neutropenia, thrombocytopenia, or anemia
- Any grade febrile neutropenia

12.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 12.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 12.3.2).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 12.1.2 for seriousness criteria), severity (see Section 12.2.3), and causality (see Section 12.2.4).

12.2.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 12.3.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 12.3.2).

12.2.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

12.2.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 9 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 9 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 12.3.2 for reporting instructions), per the definition of serious adverse event in Section 12.1.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 12.3.2 for reporting instructions), per the definition of serious adverse event in Section 12.1.2.

12.2.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 10):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 10 Causal Attribution Guidance

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

12.2.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

12.2.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF.

If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

12.2.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of

severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

12.2.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 12.3.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

12.2.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

- It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 12.2.5.3 for details on recording persistent adverse events).

12.2.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

- Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 12.2.5.3 for details on recording persistent adverse events).

12.2.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$baseline value) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 12.2.5.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 12.3.2).

12.2.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 12.2.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 12.3.2). This includes death attributed to progression of breast cancer.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

If the death is attributed to progression of cancer, “breast cancer progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 12.5.

12.2.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

12.2.5.9 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

12.2.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 12.1.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization solely for coordination of care, including hospice arrangements
- Hospitalization due solely to progression of underlying disease
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- *Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours*

12.2.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 12.1.2).

12.2.5.12 Adverse Events in Individuals Not Enrolled in the Study

If an adverse event inadvertently occurs in an individual not enrolled in the study (e.g., during administration of study drug), the Adverse Event Form provided to investigators should be completed and submitted to the Sponsor or its designee, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

12.3 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 12.1.2 for further details)
- Non-serious adverse events of special interest (see Section 12.1.3 for further details)
- Pregnancies (see Section 12.3.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/Ethics Committee (EC).

12.3.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitors: [redacted], M.D., Ph.D.

Telephone Nos.: [redacted] ([redacted] office)

[redacted] (mobile)

Email: [redacted]

Alternate Medical Monitor contact information will be provided in the study manual.

12.3.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

12.3.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators (see Section 12.3.2.2).

12.3.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 28 days after the last dose of study drug.

For the Phase Ia portion of the study, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided below.

*For the Phase Ib/IIa portion of the study, i*nvestigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the contact information below:

Phase *Ia*/Ib/IIa study:

Serious adverse events *and adverse events of special interest* should be reported to PPD *using the contact information below*.

North America:

Phone: 1.800.201.8725

Fax: 1.888.488.9697

Email: rtpsafety@ppdi.com

EMEA and Asia Pacific:

Phone: 44.1223.374.240

Fax: 44.1223.374.102

Email: EMEAASIA SafetyCentral.SM@ppdi.com

For patients in Phase Ib/IIa, once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 12.3.2.

12.3.3 Reporting Requirements for Pregnancies

12.3.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of study drug.

A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy either by faxing or by scanning and emailing to the contacts listed in Section 12.3.2.2. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

12.3.3.2 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 12.1.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

12.4 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

12.4.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

12.4.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

12.5 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

12.6 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events for the Investigational Medicinal Product (IMP) including GDC-0810 and palbociclib using the *following reference documents:*

- GDC-0810 Investigator's Brochure
- *Ibrance® US Package Insert*

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

13. PATIENT END OF TREATMENT

A patient may be discontinued from study treatment at any time if the patient, the Investigator, or the Sponsor feels that it is not in the patient's best interest to continue on study. The following is a list of possible reasons for early discontinuation of study treatment:

- Disease progression (unless there is reasonable evidence of clinical benefit to justify continuation on the protocol—to be discussed with the Sponsor)
- Any other adverse event that cannot be adequately managed with dose modifications, including dose interruption for up to 28 days
- Protocol violation requiring discontinuation of study treatment
- Patient is not compliant with study procedures
- Lost to follow-up
- Patient withdrawal of consent
- Sponsor request for early termination of study

Patients will be followed for at least 28 calendar days after the last dose of study drug. If a patient is withdrawn from treatment due to an adverse event, the patient will be followed until the adverse event has resolved or stabilized as per Section 12.4.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs*, GDC-0810 drug supply is exhausted, or when Sponsor decides to stop the study*.

14. PROTOCOL VIOLATIONS

A protocol violation occurs when the patient or Investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, patient safety, and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Dose modifications (e.g., wrong treatment or incorrect dose) that are not within the protocol specifications
- Use of a prohibited concomitant medication
- Any other deviation that presents significant risk or safety concerns to the patient

Failure to comply with GCP guidelines will also result in a protocol violation. The Sponsor, in consultation with the Investigator, will determine if a protocol violation should result in withdrawal of a patient.

When a protocol violation occurs, it will be discussed with the Investigator and appropriate forms detailing the violation will be generated. This form will be signed by representatives from the Sponsor. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

15. STATISTICAL METHODS AND CONSIDERATIONS

The objective of the Phase Ia/Ib dose escalation is to determine the MTD and/or RP2D of GDC-0810, either as single agent or in combination.

If the safety and PK profile seen in Phase Ia is deemed to be favorable, the Phase Ia will be followed by Phase IIa and Phase Ib, where different cohorts of patients will be enrolled to further assess safety, tolerability, preliminary evidence of anti-tumor activity, and exploratory PD markers of response.

15.1 PLANNED ANALYSES

Planned analyses include the analyses of safety, PK, anti-tumor activity, and data from the ^{18}FES-PET imaging correlative studies.

Due to the exploratory nature of this study, no confirmatory inferential analyses are planned, and no imputation for missing data will be done. Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment

administration/compliance, safety parameters, pharmacokinetic parameters, anti-tumor activity endpoints, and exploratory biomarkers. Data will also be displayed graphically, where appropriate. Baseline values will be defined as the closest measurement prior to the first dose of study drug, typically those collected during screening. Change from baseline will be defined as (post-baseline value – baseline value). Data will be summarized by phase/stage and dose cohorts.

15.2 DETERMINATION OF SAMPLE SIZE

15.2.1 Phase Ia

The number of patients to be enrolled in Phase Ia will depend upon the observed safety and PK/PD profile, which will determine the number of dose escalations.

The operating characteristics of the dose escalation rules are shown in Table 11 below, which provides the probability of escalation to the next higher dose for each underlying true DLT rate. For example, for a toxicity that occurs in 5% of subjects, there is a greater than 95% probability of escalating. Conversely, for a common toxicity that occurs with a rate of 70%, the probability of escalating is $<5\%$.

Table 11 Probability of Escalation to the Next Dose

True Underlying DLT Rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Escalating the Dose	97%	91%	71%	49%	31%	17%	8%	3%	1%	0.1%

Table 12 shows the probability of failing to observe toxicity in a sample size of 3 or 6 patients given various true underlying toxicity rates. For example, with 6 patients, the probability of failing to observe toxicity occurring at least 40% of the time is less than 5%.

Table 12 Probability of Failing to Observe Toxicity

True Underlying DLT Rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Failing to Observe Toxicity, N = 3	86%	73%	51%	34%	22%	13%	6.4%	2.7%	0.8%	0.01%
Probability of Failing to Observe Toxicity, N = 6	74%	53%	26%	12%	4.7%	1.6%	0.41%	<0.1%	<0.1%	<0.1%

15.2.2 Phase IIa

At the RP2D, a total of approximately 100 patients *have been* enrolled to further assess the safety, tolerability, preliminary evidence of anti-tumor activity, and exploratory PD markers of response of GDC-0810 in 3 distinct patient populations (Cohorts A1 and A2 will be combined for analysis purposes).

A total of 100 patients in Phase IIa will provide a more robust safety profile as well as sample size for preliminary assessment of anti-tumor activity based on clinical benefit rate (CBR) (see Table 13), defined as the percentage of patients achieving confirmed RECIST v1.1 defined complete response, partial response, and/or stable disease ≥24 weeks.

In Cohort A, because the presence of ESR1 mutations are associated with poor prognosis, an objective response rate (ORR), defined as the percentage of patients achieving confirmed complete and/or partial responses of at least 15% (5 out of 30 patients) would be considered of more clinical interest than CBR to warrant further development of GDC-0810 in this mutant patient population.

In Cohort B1, the desired observed CBR is 50%, based on historical CBRs of 46% (Di Leo et al. 2010) and 48% (Bachelot et al. 2012) for patients with ER+/HER2– advanced breast cancer after prior treatment with aromatase inhibitors.

In Cohort B2, the desired observed CBR is 20%, based on historical CBRs ranging from 18% to 26% for patients with ER+/HER2– advanced breast cancer after prior treatment with fulvestrant (Baselga et al. 2011; Yardley et al. 2013).

Table 13 Two-Sided Confidence Intervals for Phase IIa Cohorts

Cohort	Sample Size	Assumed Observed Effect	Confidence Level	Two-sided CI
A	N=30	15% ORR	80%	(8.34%, 28.74%)
B1	N=50	50% CBR	80%	(40.09%, 59.91%)
B2	N=20	20% CBR	80%	(9.02%, 36.07%)

15.2.3 Phase Ib

Approximately *5* patients *have been* enrolled in the Phase Ib dose escalation cohorts (Cohorts C0 *and* C1). *No additional patients will be enrolled.*

Because the dose escalation portion of Phase Ib follows the same dose escalation rules as the Phase Ia, the probability of escalation from dose level C1 to dose level C2 is also shown in Table 11. Similarly, the probability of failing to observe toxicity in dose

escalation cohorts (Cohorts C0 *and* C1) and safety run-in cohort (Cohort D1) is shown in Table 14.

*A*pproximately *4* patients *have been* enrolled at the RP2D of GDC-0810 and palbociclib*,* and approximately *6* patients *have been* enrolled at 600 mg of GDC-0810 and an LHRH agonist. With *10* patients, there is a *80*% probability of observing an adverse event with a true underlying probability of 15%.

Table 14 Probability of Safety-Signal Detection with *10* Patients

True Underlying Probability of an AE (%)	*Probability of Observing at Least 1 AE in 10 Patients (%)*
5	*40*
10	*65*
15	*80*
20	*89*

15.3 SAFETY ANALYSES

For safety analyses, the analysis population will include all enrolled patients who receive at least one dose of study medication.

Study treatment discontinuation and reasons for patient discontinuations from the study will be described and summarized. Study drug administration data will be listed and any dose modifications will be flagged.

15.3.1 Adverse Events

Adverse events will be graded according to the NCI CTCAE v4.0 and coded to preferred term and system organ class (SOC).

All adverse events reported during the adverse event reporting period will be considered as treatment-emergent adverse events. Incidence rates will be summarized with frequency and percentage by MedDRA SOC and preferred term, with all patients treated as the denominator, unless otherwise specified. In addition, adverse event incidence rates will also be summarized by severity and relationship to study drug. Treatment-related adverse events are those judged by the Investigator to be at least possibly related to the study drug. Patients with multiple occurrences of events will only be counted once at the maximum severity attributed to study drug for each preferred term, SOC, and overall.

15.3.2 Clinical Laboratory Results

Normal ranges will be used to identify values that are outside the normal ranges and abnormal laboratory results will be graded according to the NCI CTCAE v4.0.

A shift summary of baseline grade by maximum post-baseline CTCAE grade will be presented, as appropriate. For each laboratory parameter, the baseline laboratory value will be defined as the last laboratory value collected on or prior to the date of the first dose of study drug.

Patients who develop toxicities of Grade ≥ 3 will be summarized. Laboratory test results not having CTCAE grade will also be summarized. Parameters that have criteria available for both low and high values (e.g., hypercalcaemia vs. hypocalcaemia) will be summarized for both criteria. Patients will only be counted once for each criterion.

15.3.3 Vital Signs

Each vital sign (temperature, blood pressure [systolic and diastolic], respiration rate, and heart rate) will be summarized and presented by study visit. Patients with clinically significant abnormalities in vital signs as compared to baseline will be listed.

15.3.4 Concomitant Medications/Treatments

All medications and/or treatments received during the protocol treatment period will be considered as concomitant medications and/or concomitant treatments and will be coded by medical dictionary; patients who received concomitant medications and/or treatments will be listed.

15.3.5 Endometrial Thickness

Endometrial thickness changes during study as compared to baseline will be summarized and presented by study visit.

15.3.6 Ventricular Repolarization

Standard ECG intervals RR and QT will be determined for each ECG recording. Corrected QT intervals (QTc) will be determined using Fridericia's formula. Changes in ECG intervals from baseline will be calculated. Baseline is defined as either the single ECG measurement (Phase I) or the mean of the triplicate ECG measurements (Phase II) collected during screening. Standard evaluation procedures will be employed in the reading of the ECGs.

Tables to be prepared include analysis of time-matched mean differences between baseline and postdose assessments, and analysis of maximum change from baseline for each patient.

In addition, patient's QTc (Fridericia) will be categorized based on ICH E14 guidance. Tables will present the number and percentage of patients meeting or exceeding the following categories:

QTc interval prolongation

Absolute values >450 to ≤ 480 msec

Absolute values >480 to ≤ 500 msec

Absolute values >500 msec

QTc interval change from baseline

Increase from baseline >30 to ≤ 60 msec

Increase from baseline >60 msec

15.4 PHARMACOKINETIC ANALYSES

For PK analyses, the analysis population will consist of the subset of treated patients who have at least one PK sample collected.

During the Phase Ia *portion of the study*, full plasma PK profiles will be obtained for GDC-0810 and its glucuronide metabolites, and analyzed using non-compartmental methods for all patients in the dose escalation portion of the study.

In the Phase IIa portion of the study, full plasma PK profiles will be obtained for GDC-0810 and analyzed using non-compartmental methods.

In the Phase Ib portion of the study, full plasma PK profiles will be obtained for GDC-0810 and palbociclib and/or LHRH agonists and analyzed using non-compartmental methods.

In addition, in the Phase Ia/IIa/Ib, blood samples for determination of the steady-state trough concentrations (predose) of GDC-0810 will be *obtained from* all patients.

15.5 ANTI-TUMOR ACTIVITY

Objective response and clinical benefit rates will be derived according to RECIST v1.1 and summarized by dose level and cohort. Progression-free survival will be listed for all patients in Phase IIa, when appropriate.

Objective response is defined as a complete response or partial response, as determined by investigator assessment and confirmed by repeat assessment ≥ 4 weeks after initial documentation. Patients with missing baseline or no response assessments will be classified as non-responders.

CBR is defined as the percentage of patients achieving confirmed RECIST v1.1–defined complete response, partial response, and/or stable disease ≥ 24 weeks.

Progression-free survival is defined as the time from the first day of study treatment with GDC-0810 in the Phase IIa until documented disease progression or death, whichever occurs first. For patients who do not have documented progressive disease or death before the end of the study or who are lost to follow-up, progression-free survival will be censored at the day of the last tumor assessment.

15.6 EXPLORATORY STUDIES

^{18}FES-PET imaging correlative studies will be performed at baseline and after treatment to assess ER occupancy and establish correlations with anti-tumor activity and other tumor biopsy–based biomarkers of response.

Archival and biopsy tissues will be analyzed to assess correlation of efficacy with molecular markers related to the mechanism of action of GDC-0810 and include alterations in DNA mutational status, RNA expression levels, DNA copy number. and protein expression.

Matched biopsies pre- and on-treatment of safely accessible metastatic sites will be collected to assess for downstream indicators of ER target gene modulation, ER and PR protein levels, and Ki67 (tumor cell proliferation). These biomarkers will be measured at baseline and on- treatment to explore the association between changes in the tumor biomarkers as a PD readout of drug activity and objective response rate. Post-progression biopsies, whenever feasible and safely accessible, will be collected to assess for markers correlating to drug resistance.

Circulating tumor DNA will be analyzed for mutational status of*, but not limited to,* ER-α and PIK3CA to gain insights into potential causal relationships between GDC-0810's clinical activity and resistance mechanisms to endocrine therapy.

16. DATA COLLECTION, RETENTION, AND MONITORING

16.1 DATA COLLECTION INSTRUMENTS

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each patient treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a patient's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Patients will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee) but will be identified by a site number, patient number, and initials.

If a correction is required for an eCRF, the time and date stamps *will* track the person entering or updating eCRF data and *will* create an electronic audit trail.

The Investigator is responsible for reviewing all information collected on patients enrolled in this study for completeness and accuracy. A copy of the eCRF will remain at the Investigator's site at the completion of the study.

16.2 DATA MANAGEMENT PROCEDURES

The data will be entered into a validated database. The Sponsor-designated data management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 DATA QUALITY CONTROL AND REPORTING

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 ARCHIVAL OF DATA

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim and final reports), data for analysis are locked and cleaned per established procedures.

An independent radiologic review facility will be used for the purpose of collecting and assessing the quality of patient scans throughout the trial. The review facility will retain copies of scans for centralized assessments of FES-PET and tumor assessment scans.

16.5 AVAILABILITY AND RETENTION OF INVESTIGATIONAL RECORDS

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls, and reports). The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer, but at a minimum, all study

documentation must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of GDC-0810.

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

16.6 MONITORING

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

16.7 PATIENT CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

17. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S.

Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

17.1 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

17.2 *PROTOCOL DEVIATIONS*

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

17.3 INSTITUTIONAL REVIEW BOARDS OR ETHICS COMMITTEE

The protocol, Investigator's Brochure, the consent forms, any information to be given to the patient (including patient recruitment materials), and relevant supporting information must be submitted to the IRB/EC by the Investigator for review and approval before the study is initiated. The IRB's/EC's unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB, and written verification that the modification was submitted and subsequently approved should be obtained.

Investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all serious adverse events, whereas others require notification only about

events that are serious, assessed to be related to study treatment, and are unexpected.Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB and archived in the site's Study File.

Finally, the Investigator will keep the IRB/EC informed as to the progress of the study, revisions to documents originally submitted for review, annual updates, and/or request for re-approvals, and when the study has been completed.

17.3.1 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Sponsor's Sample Informed Consent Form (ICF) will be provided to each site. Sponsor or its designee must review and approve any proposed deviations from the Sample ICF or any alternate consent forms proposed by the site before IRB submission. Patients must be re-consented to the most current version of the Consent forms during their participation in the study. The final IRB-approved Consent Forms must be provided to Sponsor for regulatory purposes.

The Consent Forms must be signed by the patient before her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB-approved Informed Consent Form must be provided to Sponsor for regulatory purposes.

17.4 REPORTING OF SAFETY ISSUES AND SERIOUS BREACHES OF THE PROTOCOL OR ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority in any area of the world or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

17.5 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of GDC-0810 at any time.

If a study is prematurely terminated or discontinued, the Sponsor will promptly notify the Investigator. After notification, the Investigator must notify the respective IRB and contact all participating subjects and the hospital pharmacy (if applicable) within a 4-week time period. As directed by the Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

17.6 PUBLICATIONS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

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19. APPENDICES

Appendix 1 Schedule of Activities: Phase Ia

	Screening	PK Week Lead-In	Cycle 1				Cycle 2+ *[1]*	End of Treatment [2]	Safety Follow-Up (+ 2 days) [3]
Protocol Activities	**≤ 28 days of 1st dose**	**Day -7**	**Day 1**	**Day 8 (± 1 day)**	**Day 15 (± 1 day)**	**Day 22 (± 1 day)**	**Labs CT/MRI scans**		
Baseline Documentation									
Informed Consent	X								
Medical/Oncological History [4]	X								
Physical Examination [5]	X	X	X	X	X	X	X	X	(X)
CT/MRI Brain [6]	X								
Laboratory Studies									
Hematology and Blood Chemistry [7]	X	X	X	X	X	X	X *[1]*	X	(X)
Urinalysis [7]	X						X	X	
Circulating Tumor DNA [7]	X							X	
Trough PK Sample [8]		X		X	X	X			
GDC-0810 Dosing [9]		X	X→	→	→	→	→		
12-Lead ECG [10]	X						C2D1 (at 2 hours postdose)		
24-hr PK Assessment [11]		X [12]					C2D1 and C2D2		
Efficacy/PD Assessments									
CT/MRI Chest, Abdomen, Pelvis [13]	X						X		
Bone Scan [13]	X						X		
FES-PET/CT Scan; collect PK, E2 and SHBG samples prior to performing the scan [14]	X						C2D3; C3 if needed		
Tumor Biopsy (optional) [15]	X						C2D8 (± 1 day)		
Other Clinical Assessments									
ECOG and Vital Signs	X	X	X	X	X	X	X	X	(X)
Adverse Events/Con Meds and Treatments [16]	X	X	X	X	X	X	X	X	X

Appendix 1 Schedule of Activities: Phase Ia (cont.)

	Screening	PK Week Lead-In	Cycle 1				Cycle 2+ *[1]*	End of Treatment [1]	Safety Follow-Up (+ 2 days) [2]
Protocol Activities	**≤ 28 days of 1st dose**	**Day -7**	**Day 1**	**Day 8 (± 1 day)**	**Day 15 (± 1 day)**	**Day 22 (± 1 day)**	**Labs CT/MRI scans**		
Transvaginal Ultrasound [17]	X						*X*	X	
Study Drug Compliance [18]				X	X	X	X	X	

Study assessments may be delayed or moved ahead of the window specified to accommodate holidays, vacations, and unforeseen delays.

Footnotes

1. Cycle 2+: *To be performed per institutional guidelines and/or as clinically indicated except for ECOG, physical examination, vital signs, creatinine, liver function tests, adverse events, concomitant medication, and study drug compliance should be monitored at each cycle.*

2. End of Treatment: These assessments do not need to be completed if they have been performed within 1 week of study withdrawal (within 4 weeks for imaging studies and 3 months for the transvaginal ultrasound).

3. Safety Follow-Up: Patients should be evaluated for safety up to 28 days after the last dose of study treatment. Physical examination (including ECOG and vitals), hematology, and blood chemistry should be performed as clinically indicated. Adverse events should be followed until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later.

4. Medical/Oncological History: Includes oncologic history, demographics, history of other disease processes (active or resolved) and concomitant illnesses.

5. Physical Examination: Examination of major body systems, including known and suspected sites of disease. Height should be collected at Screening.

6. CT/MRI of the brain: To be performed as needed to rule out the presence of untreated CNS metastases.

7. Samples for hematology, blood chemistry *(except creatinine and liver function tests)*, and urinalysis will be performed *per institutional guidelines and as clinically indicated,* Circulating tumor DNA will be analyzed by a specialty laboratory. *Creatinine and liver function tests should be monitored at each cycle. ctDNA will be collected at screening and end of study visit.*

8. Trough PK Sample: Samples should be obtained **predose** on the specified days **(patient should not take the study drug at home)**. Additionally, if clinically feasible, samples should be obtained at the time of any serious and/or unusual adverse events that may be causally related to study drug.

9. GDC-0810 Dosing: GDC-0810 will be orally self-administered, except on clinic days, when they will take their daily dose at the clinic, prior to any study assessment. One cycle consists of 28 days.

10. ECG: Single 12-lead ECGs will be collected at Screening and at Cycle 2 Day 1 (at the 2-hour postdose timepoint) to assess the QTc interval. If there is QTc interval prolongation (Grade > 1), the ECG should be over read by a cardiologist at the site for confirmation.

11. 24-Hour PK Assessment: Samples will be drawn relative to time of dose at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours postdose.

Appendix 1 Schedule of Activities: Phase Ia (cont.)

12. Day -7 PK Assessment: Samples will be drawn relative to time of dose at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours postdose.
13. Tumor Imaging: CT scans of the chest, abdomen and pelvis and a bone scan will be performed to assess disease status at Screening, *and per institutional guidelines and as clinically indicated.*
14. FES-PET/CT scans: Functional ER imaging will be performed at Screening and at Cycle 2 Day 3 (between ≥ 18 and ≤ 24 hours post- evening dose from the previous day) starting at Dose Level 2 (200 mg). If needed, a third scan will be performed at Cycle 3 (same day as the tumor evaluation scans, between ≥ 2 and ≤ 12 hours postdose). If low FES uptake is observed at Screening, the investigator will determine whether the post-treatment scans are warranted. Blood samples for analysis of drug levels (PK), E2, and SHBG should be collected prior to each PET scan performed.
15. Tumor Biopsies (optional): Pre- and post-treatment biopsies from the same (whenever feasible) soft tissue or visceral metastatic lesion will be collected at Screening and Cycle 2 Day 8, between ≥ 2 and ≤ 12 hours postdose.
16. Adverse Events and Concomitant Medications/Treatments: Patients must be followed for adverse events and associated concomitant medications and treatments on a monthly basis, from the first day of study treatment until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later.
17. Transvaginal Ultrasound (if applicable): Assessment of endometrial thickness will be performed at Screening, at the end of treatment (if treated for at least 2 cycles), and as clinically indicated. Any abnormal bleeding should be evaluated with a complete gynecological workup.
18. Study Drug Compliance: GDC-0810 bottle(s) including any unused capsules should be brought to each clinic visit for drug accountability.

Appendix 2 Schedule of Activities: Phase IIa

Protocol Activities	Screening ≤ 28 days of 1st dose	Cycle 1 Day 1	Cycles 2+ *[1]* Labs Biopsies, scans	End of Treatment [2]	Safety Follow-Up (+ 2 days) [3]
Baseline Documentation					
Informed Consent	X				
Medical/Oncological History [4]	X				
Physical Examination [5]	X	X	X	X	(X)
CT/MRI Brain [6]	X				
Laboratory Studies					
Hematology and Blood Chemistry [7]	X	X	X *[1]*	X	(X)
Urinalysis [7]	X		X	X	
Circulating tumor DNA [7]	X		C3 only	X	
Pharmacogenomic sample [7]		X			
Trough PK Sample [8]		X	X (only Cycles 3, 4)		
GDC-0810 Dosing [9]		X→	X→		
Triplicate 12-Lead ECG [10]	X		Cycle 2 Day 1 predose and at 1, 2, 3, 4, 6 hours	X	
PK Sample [11]			Cycle 2 Day 1 predose and at 1, 2, 3, 4, 6 hours following dosing		
Efficacy/PD Assessments					
CT/MRI Chest, Abdomen, Pelvis [12]	X		X	X	
Bone Scan [12]	X		X	X	
FES-PET/CT Scan (Cohort A1 patients) Collect E2 and SHBG samples prior to performing the scan [13]	X		C3 and whenever disease progression is suspected		

Appendix 2 Schedule of Activities: Phase IIa (cont.)

Protocol Activities	Screening ≤ 28 days of 1st dose	Cycle 1 Day 1	Cycles 2+ *[1]* Labs Biopsies, scans	End of Treatment [1]	Safety Follow-Up (+ 2 days) [2]
Tumor Biopsy (Cohort A patients, if feasible) [14]	X				
Archival Tissue Sample (optional) [15]	X				
Other Clinical Assessments					
ECOG and Vital Signs	X	X	X	X	(X)
Adverse Events/Con Meds and Treatments [16]	X	X	X	X	X
Transvaginal Ultrasound [17]	X		X	X	
Study Drug Compliance [18]			X	X	

Study assessments may be delayed or moved ahead of the window specified to accommodate holidays, vacations, and unforeseen delays.

Footnotes

1. Cycle 2+: To be performed per institutional guidelines and/or as clinically indicated except for ECOG, physical examination, vital signs, creatinine, liver function tests, adverse events, concomitant medication, and study drug compliance should be monitored at each cycle.

2. End of Treatment: These assessments do not need to be completed if they have been performed within 1 week of study withdrawal (within 4 weeks for imaging studies and 3 months for the transvaginal ultrasound).

3. Safety Follow-Up: Patients should be evaluated for safety up to 28 days after the last dose of study treatment. Physical examination (including ECOG and vitals), hematology, and blood chemistry should be performed as clinically indicated. Adverse events should be followed up until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later.

4. Medical History: Relevant medical history includes clinically significant diseases; smoking history, use of alcohol and drugs of abuse, including history of current disease, surgeries, other pertinent clinical conditions, and information regarding underlying diseases will be recorded at screening.

5. Physical Examination: Examination of major body systems, including known and suspected sites of disease. Height should be collected at Screening.

6. CT/MRI of the brain: To be performed as needed to rule out the presence of untreated CNS metastases.

7. Samples for hematology, blood chemistry *(except creatinine and liver function tests)*, **and urinalysis** will be performed *per institutional guidelines and as clinically indicated,* Circulating tumor DNA will be analyzed by a specialty laboratory. The pharmacogenomic analysis of genes that may affect the PK of GDC-0810 and circulating tumor DNA will be analyzed at specialty laboratories. *Creatinine and liver function tests should be monitored at each cycle ctDNA will be collected at screening, Cycle 3, and end of study visit.*

8. Trough PK Sample: Plasma samples should be obtained predose on the specified days (patient should not take the study drug at home). Additionally, if clinically feasible, samples should be obtained at the time of any serious and/or unusual adverse events that may be causally related to study drug.

Appendix 2 Schedule of Activities: Phase IIa (cont.)

9. GDC-0810 Dosing: GDC-0810 will be orally self-administered within 30 minutes after eating a meal (unless specified otherwise). One cycle consists of 28 days.
10. ECG: Triplicate 12-lead ECGs will be collected approximately 2 minutes apart at Screening, on Cycle 2 Day 1 predose and at 1, 2, 3, 4, and 6 hours following dosing to assess the QTc interval. For real-time safety monitoring of patients, only one ECG printout per timepoint (of the triplicate -matched PK samples) will need to be reviewed by the investigator. For the purposes of central analysis, triplicate ECGs will be obtained in a rigorous and standardized fashion and transmitted digitally to the central reading facility for review and interpretation by specialized cardiac readers. For real-time safety monitoring of patients, only one ECG printout per timepoint (of the triplicate -matched PK samples) will need to be reviewed by the investigator. For the purposes of central analysis, triplicate ECGs will be obtained in a rigorous and standardized fashion and transmitted digitally to the central reading facility for review and interpretation by specialized cardiac readers.
11. PK Sample: PK samples will also be collected predose and at 1, 2, 3, 4, and 6 hours following dosing at Cycle 2 Day 1. If PK sampling times coincide with ECG collection times, the ECGs have to be assessed prior to PK blood collection.
12. Tumor Imaging: CT scans of the chest, abdomen and pelvis and a bone scan will be performed to assess disease status at Screening *and per institutional guidelines and as clinically indicated.*
13. FES-PET/CT scans: Functional ER imaging will be performed in all Cohort A1 patients at Screening, at Cycle 3 (per Section 11.5.1.2). If low FES uptake is observed at Screening, the investigator will determine whether the post-treatment scan(s) are warranted. Blood samples for analysis of E2 and SHBG should be collected prior to each PET scan performed.
14. Tumor Biopsies: All Cohort A patients with safely accessible soft tissue and/or visceral metastases will have tumor biopsies performed at Screening, at Cycle 2 (Day 8 for patients in Cohort A1), and if feasible, at the time when disease progression is suspected (especially if disease progression occurs prior to Cycle 3). Biopsies should be collected during the period between $\geq$ 2 and $\leq$ 12 hours postdose. Tumor Biopsies are optional but strongly encouraged for Cohort B patients with safely accessible soft tissue and/or visceral metastases.
15. Archival paraffin-embedded tissue may be collected to evaluate the histology of the tumor. If fresh tumor tissue biopsy cannot be obtained at screening, every reasonable effort should be made to obtain the most recent archival tissue sample. Tumor blocks are preferred, but in the event that local regulations prevent the shipment of tumor blocks, 15-20 unstained, serially cut slides are requested. Minimum tissue requirements are further described in the laboratory manual. Cytological, fine-needle aspiration, and decalcified bone biopsy samples are not acceptable.
16. Adverse Events and Concomitant Medications/Treatments: Patients must be followed for adverse events and associated concomitant medications and treatments on a monthly basis, from the first day of study treatment until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later.
17. Transvaginal Ultrasound (if applicable): Assessment of endometrial thickness will be performed at Screening, at the end of treatment (if treated for at least 2 cycles), and as clinically indicated. Any abnormal bleeding should be evaluated with a complete gynecological workup.
18. Study Drug Compliance: GDC-0810 bottle(s) including any unused capsules should be brought to each clinic visit for drug accountability.

Appendix 3 Schedule of Activities: Phase Ib Cohorts C0 *and* C1 (Dose Escalation)

	Screening	Cycle 1				Cycle 2		Cycle 3+ *[1]*	End of Treatment [2]	Safety Follow-Up (+ 2 days) [3]
Protocol Activities	≤ 28 days of 1st dose	Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 22 (± 1 day)	Day 1	Day 15 (± 1 day)	Labs CT/MRI scans		
Baseline Documentation										
Informed Consent	X									
Medical/Oncological History [4]	X									
Physical Examination [5]	X	X	X	X	X	X		X	X	(X)
CT/MRI Brain [6]	X									
Serum pregnancy test [7]	X									
Pharmacogenetic sample [8]	X									
Laboratory Studies										
Hematology and Blood Chemistry [9]	X	X	X	X	X	X	CBC only	X *[1]*	X	(X)
Urinalysis [9]	X							X	X	
Circulating Tumor DNA [9]	X							C3, C5	X	
Trough PK Sample [10]						X		C3, C4	X	
GDC-0810 Dosing [11]		X→	→	→	→	→	→	→		
Pa bociclib Dosing [12]		X	→	→		→	→	→		
12-Lead ECG [13]	X	X				X		As clinically indicated	X	
PK Assessment [14]		predose and at 1, 2, 3, 4, 6 hours following dosing	predose and at 1, 2, 3, 4, 6 hours following dosing							

Appendix 3 Schedule of Activities: Phase Ib Cohorts C0 and C1 (Dose Escalation) **(cont.)**

	Screening	Cycle 1				Cycle 2		Cycle 3+ *[1]*	End of Treatment [1]	Safety Follow-Up (+ 2 days) [2]
Protocol Activities	**≤ 28 days of 1st dose**	**Day 1**	**Day 8 (± 1 day)**	**Day 15 (± 1 day)**	**Day 22 (± 1 day)**	**Day 1**	**Day 15 (± 1 day)**	**Labs CT/MRI scans**		
Efficacy/PD Assessments										
CT/MRI Chest, Abdomen, Pelvis [15]	X							X		
Bone Scan [16]	X							X		
Tumor Biopsy (mandatory) [16]	X			X					X	
Archival Tissue Sample (optional) [17]	X									
Other Clinical Assessments										
ECOG and Vital Signs	X	X	X	X	X	X		X	X	(X)
Adverse Events/Con Meds and Treatments [18]	X	X	X	X	X	X		X	X	X
Transvaginal Ultrasound [19]	X							X	X	
Study Drug Compliance [20]			X	X	X	X		X	X	
For pre-/peri-menopausal patients only: LHRH agonist [21]	administration at least 4 weeks before study treatment start	Administration every 28 days								

Study assessments may be delayed or moved ahead of the window specified to accommodate holidays, vacations, and unforeseen delays.

Footnotes

1. Cycle 3+: To be performed per institutional guidelines and/or as clinically indicated except for ECOG, physical examination, vital signs, creatinine, liver function tests, adverse events, concomitant medication, and study drug compliance should be monitored at each cycle. Patients receiving GDC-0810 in combination with palbociblib will have hematology collected at least monthly and as clinically indicated.

2. End of Treatment: These assessments do not need to be completed if they have been performed within 1 week of study withdrawal (within 4 weeks for imaging studies and 3 months for the transvaginal ultrasound).

3. Safety Follow-Up: Patients should be evaluated for safety up to 28 days after the last dose of study treatment. Physical examination (including ECOG and vitals), hematology, and blood chemistry should be performed as clinically indicated. Adverse events should be followed until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later.

Appendix 3 Schedule of Activities: Phase Ib Cohorts C0 and C1 (Dose **Escalation) (cont.)**

4. Medical/Oncological History: Includes oncologic history, demographics, history of other disease processes (active or resolved) and concomitant illnesses.
5. Physical Examination: Examination of major body systems, including known and suspected sites of disease. Height should be collected at Screening.
6. CT/MRI of the brain: To be performed as needed to rule out the presence of untreated CNS metastases.
7. Serum pregnancy test (for patients on LHRH agonists) must be performed and documented as negative within 14 days prior to Cycle 1, Day 1.
8. A pharmacogenomic sample will be collection prior to Cycle 1 Day 1. The pharmacogenomic analysis of genes that may affect the PK of GDC-0810 and circulating tumor DNA will be analyzed at specialty laboratories.
9. Samples for hematology, blood chemistry ***(except creatinine and liver function tests)*****, and urinalysis** will be performed *per institutional guidelines and as clinically indicated,* Circulating tumor DNA will be collected at screening C3, C5, and at progression and analyzed by a specialty laboratory. At Cycle 2 Day 15 collection of a complete blood count is required only. *Creatinine and liver function tests should be monitored at each cycle.*
10. Trough PK Sample: Samples should be obtained **predose** on the specified days **(patient should not take the study drug at home)**. Additionally, if clinically feasible, samples should be obtained at the time of any serious and/or unusual adverse events that may be causally related to study drug.
11. GDC-0810 Dosing: GDC-0810 will be orally self-administered within 30 minutes after eating a meal (unless specified otherwise), except on clinic days, when the daily dose will be taken at the clinic, prior to any study assessment. One cycle consists of 28 days.
12. Palbociclib Dosing: Palbociclib will be orally self-administered on Days 1-21 of each cycle, except on clinic days, when the daily dose will be taken at the clinic, prior to any study assessment. One cycle consists of 28 days.
13. ECG: Single ECGs will be collected at Screening, Cycle 1 Day 1 (prior to first dose), Cycle 2 Day 1 and end of treatment visits. At other study visits they should be recorded as clinically indicated. If there is QTc interval prolongation (Grade >1), the ECG should be over read by a cardiologist at the site for confirmation.
14. PK Assessment: Samples will be drawn relative to time of dose at 0 (predose), 1, 2, 3, 4, 6 hours , post-dose at Cycle 1 Day 1 and Cycle 1 Day 8.
15. Tumor Imaging: CT scans of the chest, abdomen and pelvis and a bone scan will be performed to assess disease status at Screening *and per institutional guidelines and as clinically indicated.*
16. Tumor Biopsies : Pre-, on- treatment and post-progression biopsies from the same (whenever feasible) soft tissue or visceral metastatic lesion that is safely accessible will be collected at Screening, Cycle1 Day 15, between ≥ 2 and ≤ 12 hours post-dose, and at the time of progression.

Appendix 3 Schedule of Activities: Phase Ib Cohorts C0 and C1 (Dose Escalation) **(cont.)**

17. Archival paraffin-embedded tissue may be collected to evaluate the histology of the tumor. If fresh tumor tissue biopsy cannot be obtained at screening, every reasonable effort should be made to obtain the most recent archival tissue sample. Tumor blocks are preferred, but in the event that local regulations prevent the shipment of tumor blocks, 15-20 unstained, serially cut slides are requested. Minimum tissue requirements are further described in the laboratory manual. Cytological, fine-needle aspiration, and decalcified bone biopsy samples are not acceptable.
18. Adverse Events and Concomitant Medications/Treatments: Patients must be followed for adverse events and associated concomitant medications and treatments *at each clinic visit* on a monthly basis, from the first day of study treatment until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later.
19. Transvaginal Ultrasound (if applicable): Assessment of endometrial thickness will be performed at Screening, at the end of treatment (if treated for at least 2 cycles), and as clinically indicated. Any abnormal bleeding should be evaluated with a complete gynecological workup.
20. Study Drug Compliance: GDC-0810 and palbociclib bottle(s) including any unused capsules should be brought to each clinic visit for drug accountability.
21. LHRH agonist (if applicable): Treatment with LHRH agonist as per local practice for all women who are pre- or peri-menopausal at study entry. Patients must have commenced treatment with LHRH agonist at least 4 weeks prior to study entry. It is recommended to administer the LHRH agonist (given every 28 days) on-site. If LHRH agonist is administered at home by the patient, a patient diary will be implemented.

Appendix 4 Schedule of Activities: Phase Ib Cohort D1 (Safety Run-In)

	Screening	Cycle 1				Cycle 2+		End of Treatment [1]	Safety Follow-Up (+ 2 days) [2]
Protocol Activities	**≤ 28 days of 1st dose**	**Day 1**	**Day 8 (± 1 day)**	**Day 15 (± 1 day)**	**Day 22 (± 1 day)**	**Day 1**	**Labs CT/MRI scans *[3]***		
Baseline Documentation									
Informed Consent	X								
Medical/Oncological History [4]	X								
Physical Examination [5]	X	X	X	X	X	X	X	X	(X)
Serum pregnancy test [6]	X								
Pharmacogenetic sample [7]	X								
CT/MRI Brain [8]	X								
Laboratory Studies									
Hematology and Blood Chemistry [9]	X	X	X	X	X	X	X *[3]*	X	(X)
Urinalysis [9]	X						X	X	
Circulating Tumor DNA [9]	X						C3, C5	X	
Trough PK Sample [10]						C3, C4		X	
GDC-0810 Dosing [11]		X→	→	→	→	→	→		
LHRH Dosing [12]		X				X			
12 lead ECG [13]	X	X				X	As clinically indicated	x	
PK Assessment [13]		predose and at 1, 2, 3, 4, 6 hours following dosing				predose and at 1, 2, 3, 4, 6 hours following dosing			

Appendix 4 Schedule of Activities: Phase Ib Cohort D1 (Safety Run-In) (cont.)

	Screening	Cycle 1				Cycle 2+		End of Treatment [1]	Safety Follow-Up (+ 2 days) [2]
Protocol Activities	≤ 28 days of 1st dose	Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 22 (± 1 day)	Day 1	Labs CT/MRI scans *[3]*		
Efficacy/PD Assessments									
CT/MRI Chest, Abdomen, Pelvis [14]	X						X		
Bone Scan [15]	X						X		
Tumor Biopsy (mandatory) [16]	X			C1D15 (± 1 day)				X	
Archival Tissue Sample (optional) [17]	X								
Other Clinical Assessments									
ECOG and Vital Signs	X	X	X	X	X	X	X	X	(X)
Adverse Events/Con Meds and Treatments [18]	X	X	X	X	X	X	X	X	X
Transvaginal Ultrasound [19]	X						X	X	
Study Drug Compliance [20]			X	X	X	X	X	X	

Study assessments may be delayed or moved ahead of the window specified to accommodate holidays, vacations, and unforeseen delays.

Footnotes

1. End of Treatment: These assessments do not need to be completed if they have been performed within 1 week of study withdrawal (within 4 weeks for imaging studies and 3 months for the transvaginal ultrasound).

2. Safety Follow-Up: Patients should be evaluated for safety up to 28 days after the last dose of study treatment. Physical examination (including ECOG and vitals), hematology, and blood chemistry should be performed as clinically indicated. Adverse events should be followed up until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later.

3. Cycle 2+, Labs, CT/MRI scans: To be performed per institutional guidelines and/or as clinically indicated except for ECOG, physical examination, vital signs, creatinine, liver function tests, adverse events, concomitant medication, and study drug compliance should be monitored at each cycle.

4. Medical History: Relevant medical history includes clinically significant diseases; smoking history, use of alcohol and drugs of abuse, including history of current disease, surgeries, other pertinent clinical conditions, and information regarding underlying diseases will be recorded at screening.

Appendix 4 Schedule of Activities: Phase Ib Cohort D1 (Safety Run-In) **(cont.)**

5. Physical Examination: Examination of major body systems, including known and suspected sites of disease. Height should be collected at Screening.
6. Serum pregnancy test (for patients on LHRH agonists) must be performed and documented as negative within 14 days prior to Cycle 1, Day 1.
7. A pharmacogenomic sample will be collection prior to Cycle 1 Day 1. The pharmacogenomic analysis of genes that may affect the PK of GDC-0810 and circulating tumor DNA will be analyzed at specialty laboratories.
8. CT/MRI of the brain: To be performed as needed to rule out the presence of untreated CNS metastases.
9. Samples for hematology, blood chemistry ***(except creatinine and liver function tests)*****, and urinalysis** will be performed *per institutional guidelines and as clinically indicated,* Circulating tumor DNA will be collected at screening C3, C5, and at disease progression and will be analyzed by a specialty laboratory. *Creatinine and liver function tests should be monitored at each cycle.*
10. Trough PK Sample: Plasma samples should be obtained pre-dose on the specified days (patient should not take the study drug at home). Additionally, if clinically feasible, samples should be obtained at the time of any serious and/or unusual adverse events that may be causally related to study drug.
11. GDC-0810 Dosing: GDC-0810 will be orally self-administered within 30 minutes after eating a meal (unless specified otherwise). One cycle consists of 28 days.
12. LHRH agonist Dosing: Treatment with LHRH agonist as per local practice for all women who are pre- or peri-menopausal at study. Patients must have commenced treatment with LHRH agonist at least 4 weeks prior to study entry. It is recommended to administer the LHRH agonist (given every 28 days) on-site. If LHRH agonist is administered at home by the patient, a patient diary will be implemented.
13. ECG: Single ECGs will be collected at Screening, Cycle 1 Day 1 (prior to first dose), Cycle 2 Day 1 and end of treatment visits. At other study visits they should be recorded as clinically indicated. If there is QTc interval prolongation (Grade > 1), the ECG should be over read by a cardiologist at the site for confirmation.
14. PK Sample: PK samples will also be collected pre-dose and at 1, 2, 3, 4, and 6 hours following dosing at Cycle 1 Day *1* and Cycle *2* Day 1. If PK sampling times coincide with ECG collection times, the ECGs have to be assessed prior to PK blood collection.
15. Tumor Imaging: CT scans of the chest, abdomen and pelvis and a bone scan will be performed to assess disease status at Screening *and per institutional guidelines and as clinically indicated.*
16. Tumor Biopsies: Patients with safely accessible soft tissue and/or visceral metastases will have tumor biopsies performed at Screening, at Cycle 1 Day 15 and if feasible, at the time when disease progression is suspected (especially if disease progression occurs prior to Cycle 3). Biopsies should be collected during the period between ≥ 2 and ≤ 12 hours post-dose.

Appendix 4 Schedule of Activities: Phase Ib Cohort D1 (Safety Run-In) **(cont.)**

17. Archival Tissue Sample: Archival paraffin-embedded tissue may be collected to evaluate the histology of the tumor. If fresh tumor tissue biopsy cannot be obtained at screening, every reasonable effort should be made to obtain the most recent archival tissue sample. Tumor blocks are preferred, but in the event that local regulations prevent the shipment of tumor blocks, 15-20 unstained, serially cut slides are requested. Minimum tissue requirements are further described in the laboratory manual. Cytological, fine-needle aspiration, and decalcified bone biopsy samples are not acceptable.
18. Adverse Events and Concomitant Medications/Treatments: Patients must be followed for adverse events and associated concomitant medications and treatments on a monthly basis, from the first day of study treatment until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later.
19. Transvaginal Ultrasound (if applicable): Assessment of endometrial thickness will be performed at Screening, at the end of treatment (if treated for at least 2 cycles), and as clinically indicated. Any abnormal bleeding should be evaluated with a complete gynecological workup.
20. Study Drug Compliance: GDC-0810 bottle(s) including any unused capsules should be brought to each clinic visit for drug accountability.

Appendix 5 Laboratory Tests

Hematology	Chemistry	Other
Hemoglobin	Total bilirubin [a]	Urinalysis (dipstick)
Platelet count	Alanine transaminase (ALT) [a]	Estradiol (E2)
Red blood cell count	Aspartate transaminase (AST) [a]	Sex hormone-binding globulin (SHBG)
White blood cell count	Alkaline phosphatase	
White blood cell differential	Total protein	
	Albumin	
	Sodium	
	Potassium	
	Chloride	
	Calcium	
	Phosphorus	
	Magnesium	
	Blood urea nitrogen (BUN)	
	Creatinine [a]	
	Uric acid	
	Glucose	
	Lactase dehydrogenase (LDH)	

[a] *Required laboratory test.*

Laboratory test are obtained as described in the Schedule of Assessments.

Appendix 6 ECOG Performance Status

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

Appendix 7 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCE (Version 4.0) may be reviewed online at the following NCI website:

http://ctep.cancer.gov/reporting/ctc.html

Appendix 8 Restricted Medications or Treatments

a. The following drugs are sensitive substrates or substrates of CYPs 2B6, 2C8, 2C9, 2C19 and 3A with a narrow therapeutic window. It is strongly recommended to consider alternate therapies, whenever possible. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, refer to the appropriate product label.

CYP Enzymes	Sensitive Substrates	Substrates with Narrow Therapeutic Range
CYP2B6	Bupropion, efavirenz	
CYP2C8	Repaglinide	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin (neither drug should be used concomitantly with GDC-0810)
CYP2C19	Clobazam, lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

b. The following drugs are strong inhibitors of CYP3A. It is strongly recommended to avoid concomitant use of strong CYP3A inhibitors with IBRANCE (palbociclib) and to avoid grapefruit or grapefruit juice during IBRANCE treatment. If coadministration of IBRANCE with a strong CYP3A inhibitor cannot be avoided, reduce the dose of IBRANCE. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, refer to the appropriate product label.

CYP Enzymes	Strong Inhibitors
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

c. The following drugs are strong and moderate inducers of CYP3A. It is strongly recommended to avoid concomitant use of strong and moderate inducers of CYP3A with IBRANCE (palbociclib). It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, refer to the appropriate product label.

CYP Enzymes	Strong Inducers	Moderate Inducers
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin