Official Title: A Phase II, Open-Label, Randomized Study of GDC-0810 Versus Fulvestrant in Postmenopausal Women With Advanced or Metastatic ER+ /HER2- Breast Cancer Resistant to Aromatase Inhibitor Therapy

NCT Number: NCT02569801

Document Date: Protocol Version 2: 24-January-2017

PROTOCOL

TITLE:	**A PHASE II, OPEN-LABEL, RANDOMIZED STUDY OF GDC-0810 VERSUS FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ADVANCED OR METASTATIC ER+/HER2−BREAST CANCER RESISTANT TO AROMATASE INHIBITOR THERAPY**
PROTOCOL NUMBER:	GO29689
VERSION NUMBER:	*2*
EUDRACT NUMBER:	2015-000106-19
IND NUMBER:	116019
TEST PRODUCT:	GDC-0810 (RO7056118)
MEDICAL MONITOR:	[redacted], *M.D., Ph.D.*
SPONSOR:	Genentech, Inc.
DATE FINAL:	*Version 1: 27 May 2015* *Version 2:* See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Jan-2017 17:11:42

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol GO29689 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. The decision to halt the development of GDC-0810 is not due to safety concerns. Following the halt of enrollment, the study team was unblinded and therefore monitoring of active patients can be conducted by the Medical Monitor. The Internal Monitoring Committee (IMC) will no longer be required to monitor ongoing efficacy and safety, given the IMC concluded that safety profiles observed from patients treated in Study GO29689 were consistent with the known safety profiles for GDC-0810 and fulvestrant and no new safety findings had been identified. The Sponsor will continue to monitor clinical safety data in real time.

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

- Enrollment 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 fulvestrant until progression of disease, unacceptable toxicity, consent withdrawal, GDC-0810 drug supply has been exhausted, or the Sponsor terminates the study.
- Limited physical examination, vital signs, liver function test, creatinine adverse events, concomitant medication, and study drug compliance will be collected at least monthly and as clinically indicated.
- Hematology, ECOG, 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.
- Patient-reported outcome questionnaires will be discontinued.
- Survival information from patients who discontinued from the treatment phase of the study will no longer be collected.
- The IMC will longer be required to monitor ongoing patient safety.
- The Sponsor will continue to monitor clinical safety data in real time.
- 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.
- Based on accumulated clinical experience and the addition of elevation of hepatic transaminases as a potential risk in the GDC-0810 Investigator's Brochure, Version 3, Grade ≥3 elevation of ALT or AST has been added as adverse event of special interest to align with the other ongoing GDC-0810 study (GO29642).

- Clinical and nonclinical summaries have been update to align with the GDC-0810 Investigator's Brochure, Version 4.

  Note: Exclusion criteria were not updated to align with GDC-0810 Investigator's Brochure recommendations given discontinuation of study enrollment.
- The definition of the end of study has been revised because of the Sponsor's decision to halt the development of GDC-0810 (see Section 3.2).
- 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:	**A PHASE II, OPEN-LABEL, RANDOMIZED STUDY OF GDC-0810 VERSUS FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ADVANCED OR METASTATIC ER+/HER2− BREAST CANCER RESISTANT TO AROMATASE INHIBITOR THERAPY**
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TEST PRODUCT:	GDC-0810 (RO7056118)
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 for your study files. Please return a copy to PPD at the address provided in your study binder.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, OPEN-LABEL, RANDOMIZED STUDY OF GDC-0810 VERSUS FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ADVANCED OR METASTATIC ER+/HER2− BREAST CANCER RESISTANT TO AROMATASE INHIBITOR THERAPY**
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EUDRACT NUMBER:	2015-000106-19
IND NUMBER:	116019
TEST PRODUCT:	GDC-0810 (RO7056118)
PHASE:	II
INDICATION:	Advanced or Metastatic ER+/HER2− Breast Cancer
SPONSOR:	Genentech, Inc.

Objectives

The development of GDC-0810 has been halted and enrollment discontinued; therefore, the primary objectives will not be met.

Efficacy Objectives

The co-primary efficacy objectives for this study are as follows:

- To evaluate the efficacy of GDC-0810 compared with fulvestrant in the intent-to-treat (ITT) population as measured by progression-free survival (PFS)
- To evaluate the efficacy of GDC-0810 compared with fulvestrant in patients with detectable *ESR1* mutations as measured by PFS

The secondary efficacy objective for this study is as follows:

- To assess the clinical activity of GDC-0810 versus fulvestrant, as measured by objective response rate (ORR), duration of response (DOR), clinical benefit rate (CBR), and overall survival (OS)

Safety Objectives

The safety objective for this study is as follows:

- To evaluate the safety and tolerability of GDC-0810 compared with fulvestrant, focusing on the nature, frequency, and severity of serious and non-serious adverse events

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is as follows:

- To assess the pharmacokinetics of GDC-0810 in patients with advanced or MBC resistant to aromatase inhibitor (AI) therapy

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To estimate the frequency of *ESR1* mutations in patients with advanced or metastatic breast cancer (MBC) resistant to AI therapy
- To assess the potential relationship between GDC-0810 exposure (as measured by PK variables) and tumor response

- To assess the potential relationship between GDC-0810 exposure (as measured by PK variables) and safety
- To assess disease and treatment-related symptoms, patient function, and health status/health-related quality of life (HRQoL) with GDC-0810 and fulvestrant as measured by the European Organization for Research and Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and its breast cancer module (QLQ-BR23)
- To evaluate patients' treatment satisfaction with medication using a modified version of the Treatment Satisfaction Questionnaire for Medication (TSQM) for use in breast cancer
- To assess whether dynamic (non-inherited) biomarkers, including but not limited to estrogen receptor (ER)/progesterone receptor (PgR)/human epidermal growth factor receptor 2 (HER2) expression, luminal A/B status, *PIK3CA* mutations, *AKT1* mutations, *p53* mutations, Ki67 levels, ER target gene expression and PI3K target gene expression, are predictive of response to study treatment, susceptibility to developing adverse events, or progression to a more severe disease state, can provide evidence of treatment activity, or can increase the knowledge and understanding of disease biology
- When post-progression tissue is available, to evaluate the relationship between GDC-0810 exposure and changes in levels of biomarkers, including but not limited to the dynamic (non-inherited) biomarkers described above
- To use whole genome sequencing to assess whether non-dynamic (inherited) polymorphisms in the genome might be predictive of response to study treatment, susceptibility to developing adverse events, or progression to a more severe disease state, or can increase the knowledge and understanding of disease biology
- To explore the role of polymorphisms in drug metabolism enzyme and transporter genes in the pharmacokinetics, safety, and efficacy of GDC-0810 in patients with advanced or MBC, if indicated by PK data

Study Design

Description of Study

This is a multicenter, international, randomized, open-label, Phase II trial with two study arms. A total of approximately 152 patients with advanced or metastatic ER + /HER2 − breast cancer who have experienced recurrence or progression of their disease while receiving AI therapy for advanced or metastatic disease or who have relapsed within 6 months after completing adjuvant AI therapy will be enrolled in this study. Patients who are enrolled in Arm A will receive GDC-0810, administered at 600 mg by mouth (PO) daily. Patients who are enrolled in Arm B will receive fulvestrant, administered at 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and Day 1 of each subsequent 28-day cycle thereafter.

A permuted block randomization scheme will be used to ensure an approximate 1:1 allocation of patients who receive GDC-0810 (Arm A) versus patients who receive fulvestrant (Arm B) with respect to two stratification factors per local assessment: geographic region (United States, European Union, and Rest of World) and presence or absence of visceral disease.

Patients may have either measurable disease (per Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST v1.1]) and/or non-measurable, but evaluable, locally advanced or metastatic disease with at least one evaluable bone lesion. Locally advanced disease must not be amenable to resection or other local therapy with curative intent.

Patients will receive study treatment in 28-day cycles until documented radiographic disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination. Tumor assessments will be conducted for all patients at screening, *per institutional guidelines, and as clinically indicated.*

Enrollment in Study GO29689 has been discontinued; therefore, no further patients will be enrolled in this study. Any patient currently enrolled in Study GO28689 experiencing clinical benefit may continue to receive GDC-0810 as a single agent or fulvestrant until disease progression (as assessed by the investigator based on radiographic findings or clinical symptoms), unmanageable toxicity, patient withdrawal of consent, GDC-0810 drug supply has been exhausted, or the Sponsor terminates the study. All patients who are discontinued from study treatment will return for a study drug discontinuation visit within *30* days after the last

dose of study treatment and will be followed for adverse events for at least 28 days after the last dose of study treatment.

Number of Patients

A total of approximately 152 patients with advanced or metastatic ER+/HER2− breast cancer who have experienced recurrence or progression of their disease while receiving AI therapy for advanced or metastatic disease or who have relapsed within 6 months after completing adjuvant AI therapy will be enrolled in this study.

Target Population

Patients with ER+ HER2−, locally advanced or MBC will be enrolled in the study.

Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-Specific Inclusion Criteria

- Postmenopausal women with histologically or cytologically confirmed invasive, ER+/HER2− (defined by local guidelines) metastatic or inoperable (not amenable to resection or other local therapy with curative intent), locally advanced breast cancer

  Postmenopausal is defined as meeting at least one of the following criteria:

  - Prior bilateral oophorectomy
  - Age ≥ 56 years and 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 after 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 after medical menopause on luteinizing hormone-releasing hormone (LHRH) agonist (on stable dose ≥ 1 year), with amenorrhea ≥ 1 year since last menses and serum estradiol levels (< 20 pg/mL) in the postmenopausal range irrespective of FSH/LH levels
  - Women with therapy-induced amenorrhea must agree to remain abstinent or use single or combined non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of GDC-0810 or at least $1\ year$ after the last dose of fulvestrant. Abstinence is only acceptable if it is in line with 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.
  - Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.
- Patients for whom endocrine therapy (e.g., fulvestrant) is recommended and treatment with cytotoxic chemotherapy is not indicated at time of entry into the study, as per national or local treatment guidelines
- Radiologic/objective evidence of recurrence or progression to the most recent systemic therapy for breast cancer
- Radiologic/objective evidence of breast cancer recurrence or progression while on or within 6 months after the end of adjuvant treatment with an AI, or progression while on or within 1 month after the end of prior AI treatment for locally advanced or MBC. The AI (letrozole, anastrozole, or exemestane) does not have to be the most recent treatment before randomization, but patients must have received at least 4 weeks of treatment with an AI.

- Patients must have measurable disease by RECIST v1.1 or non-measurable, evaluable disease with at least one evaluable bone lesion by RECIST v1.1 based on radiologic scans within 28 days of Day 1 of Cycle 1. Bone lesions that have been irradiated are not evaluable.

General Inclusion Criteria

- Signed Informed Consent Form
- Age $\geq$ 18 years
- ECOG Performance Status of 0 or 1
- Consent to the collection of a formalin-fixed paraffin-embedded (FFPE) block or a minimum of 10 freshly cut unstained tumor slides (submission of 15–20 is strongly encouraged) from archival tumor tissue or a newly collected ("fresh") tumor sample for protocol-mandated exploratory assessments
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 days prior to Day 1 of Cycle 1:
  - Absolute neutrophil count $\geq$ 1500/μL
  - Platelet count $\geq$ 90,000/μL
  - Hemoglobin $\geq$ 9.0 g/dL (90 g/L)
  - Albumin $\geq$ 3.0 g/dL (30 μmol/L)
  - Total bilirubin $\leq$ 1.5 $\times$ upper limit of normal (ULN)
  - Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) $\leq$ 1.5 $\times$ ULN, with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq$ 5.0 $\times$ ULN

    Patients with documented bone metastases: ALP $\leq$ 5.0 $\times$ ULN

    Serum creatinine $\leq$ 1.5 $\times$ ULN or creatinine clearance $\geq$ 50 mL/min based on Cockroft–Gault glomerular filtration rate (GFR) estimation

    $$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine})}$$

    International normalized ratio (INR) < 1.5 and activated partial thromboplastin time (aPTT) < 1.5 $\times$ ULN; for patients requiring therapeutic anticoagulation therapy, a stable INR $\leq$ 2.5

Exclusion Criteria

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

Disease-Specific Exclusion Criteria

- HER2-positive disease (immunohistochemistry [IHC] 3 + staining, fluorescence in situ hybridization [FISH] positive, and/or chromogenic in situ hybridization [CISH] positive)
- Prior treatment with fulvestrant
- Prior anti-cancer therapy within 2 weeks prior to Cycle 1 Day 1
- Prior radiation therapy within 2 weeks prior to Cycle 1 Day 1
- Prior treatment with > 1 cytotoxic chemotherapy regimens or > 2 endocrine therapies for advanced or metastatic disease
- Ongoing, acute treatment-related toxicity that has not resolved to Grade $\leq$ 1 or been deemed stable by the investigator
- Concurrent hormone replacement therapy
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy; use of bisphosphonate therapy or denosumab for other reasons (e.g., bone metastasis, osteoporosis, etc.) is allowed.
- Known untreated or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control); a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will be performed at screening if required by the local health authority

Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:

  - Evaluable or measurable disease outside the CNS is present.
  - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - Screening CNS radiographic study is ≥ 8 weeks since completion of radiotherapy and ≥ 4 weeks since the discontinuation of corticosteroids
- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence; patients with slow-growing, benign tumors are allowed

General Exclusion Criteria

- Inability or unwillingness to swallow pills or receive IM injections
- History of malabsorption syndrome, short bowel syndrome, gastric resection, or other condition that would interfere with enteral absorption
- History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)
- Active bowel inflammation (e.g., diverticulitis)
- History of endometrial cancer or atypical endometrial hyperplasia
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or current known active infection with hepatitis B virus (HBV), or hepatitis C virus (HCV)

  Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [anti-HBc]) or hepatitis C (HCV antibody). Unless required by local regulations, patients are not required to have HIV, HBV, or HCV assessments at screening if these assessments have not been previously performed.

  - Patients who are positive for anti-HBc are eligible only if testing is also positive for hepatitis B surface antibody and polymerase chain reaction (PCR) is negative for HBV DNA.
  - Patients who are positive for HCV serology are eligible only if testing for HCV RNA is negative.
- Active autoimmune disease that is not controlled for at least 6 months by stable doses of nonsteroidal or steroidal (< 10 mg of prednisone per day) anti-inflammatory drugs or active inflammatory disease, including small or large intestine inflammation such as Crohn's disease or ulcerative colitis, which requires immunosuppressive therapy
- Clinically significant cardiac or pulmonary dysfunction, including the following:
  - Current uncontrolled Grade ≥ 2 hypertension or unstable angina
  - Symptomatic congestive heart failure of New York Heart Association Class II, III or IV
  - Serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia or conduction abnormality that has been treated and for which the patient is no longer at risk for serious arrhythmia (e.g., Wolff-Parkinson-White syndrome treated with surgical ablation)
  - History of acute coronary syndrome or unstable angina within 6 months prior to Cycle 1, Day 1
- History of congenital long QT syndrome or corrected QT interval (QTcF) > 470 msec
- Immunocompromised status due to current known active infection with HIV or due to the use of immunosuppressive therapies for other conditions
- Need for current chronic corticosteroid therapy (≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)

- Inhaled corticosteroids are allowed
- Pregnancy, lactation, or breastfeeding
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
- Major surgical procedure or significant traumatic injury within 28 days prior to Day 1 of Cycle 1 or anticipation of the need for major surgery during the course of study treatment
- Inability, in the opinion of the investigator, to comply with study and follow-up procedures

Length of Study

The enrollment duration is projected to be approximately 22 months after the first patient is enrolled. The last PFS event for the primary PFS analysis is projected to occur approximately 26 months after the first patient is enrolled.

End of Study

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

Outcome Measures

Primary Efficacy Outcome Measures

The primary efficacy outcome measures for this study, for all patients as well as the subset of patients with *ESR1* mutations, are as follows:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator per RECIST v1.1 or death from any cause on study, whichever occurs first

Secondary Efficacy Outcome Measures

The secondary outcome measures for this study are the following:

- OS, defined as the time from randomization to the time of death from any cause
- Objective response (PR plus complete response [CR]) as determined by the investigator per RECIST v1.1
- DOR, defined as the time from the first occurrence of a documented objective response until first observation of disease progression, as determined by the investigator per RECIST v1.1, or death from any cause on study, whichever occurs first
- Clinical benefit, defined as PR, CR, or stable disease (SD), lasting for at least 24 weeks from the time of randomization

Safety Outcome Measures

The safety and tolerability of GDC-0810 will be assessed using the following:

- The incidence, nature, and severity of adverse events reported during the adverse event reporting period, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE, v4.0)
- Incidence, nature and severity of serious adverse events
- Incidence of adverse events leading to study treatment discontinuation, modification or interruption
- Clinically significant changes in vital signs, physical findings, and clinical laboratory results during and following GDC-0810 or fulvestrant administration during the adverse-event reporting period

Pharmacokinetic Outcome Measures

Sparse PK samples will be collected and *may* be analyzed using population PK methods to estimate apparent clearance, volume of distribution, absorption rate constant, and other appropriate measures as data allow*, and plasma concentrations will be summarized by visit.*

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Assessment of RNA in pre- and post-treatment tumor specimens, including assessment of PI3K and ER target gene expression signatures, ER, PgR, and HER2 status and luminal A/B status
- Alterations of DNA in pre- and post-treatment tumor specimens, including *ESR1* mutations, *PIK3CA* mutations, *AKT1* mutations, and *TP53* mutations
- Assessment of Ki67 levels in pre- and post-treatment tumor specimens
- Alterations in ctDNA from peripheral blood, including but not limited to *ESR1, PIK3CA* and *AKT1*
- Assessment of mean change in disease/treatment-related symptoms, function and health status/HRQoL scales of the EORTC QLQ-C30 and the EORTC QLQ-BR23 breast module
- Assessment of mean treatment satisfaction on the subscales (side effects, convenience, and global satisfaction) of a modified version of the TSQM
- Whole genome sequencing data will be analyzed in the context of this study and explored in aggregate with other studies to better understand disease pathobiology and guide the development of new therapeutic approaches. Given the complexity and exploratory nature of these analyses, whole genome sequencing data and analyses will not be shared with investigators or study participants unless required by law.

Investigational Medicinal Products

Test Product (Investigational Drug)

The test product for this study is GDC-0810. GDC-0810 will be supplied by the Sponsor as white oblong tablets containing 200 mg GDC-0810 free acid. The 600-mg dose of GDC-0810 will be taken orally once per day until disease progression or intolerable toxicity. GDC-0810 is supplied as 200-mg tablets; therefore, patients will take three 200-mg tablets daily to receive a 600-mg dose. Each 600-mg dose should be taken within 30 minutes after a meal, and efforts should be made by patients to take the dose at the same approximate time each day. If a dose is missed (i.e., not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Comparator

The comparator for this study is fulvestrant. Fulvestrant will be supplied by the Sponsor per country-specific requirements. For countries in which the Sponsor is supplying fulvestrant, it will be supplied in sterile, single-patient, prefilled syringes containing 50 mg/mL fulvestrant as a 5-mL injection. Fulvestrant 500 mg will be administered in the clinic as two intramuscular injections of 250 mg each on Cycle 1 Days 1 and 15 and Day 1 of each subsequent 28-day cycle.

Non-Investigational Medicinal Products

None

Statistical Methods

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

Primary Analysis

The primary efficacy endpoint is PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments using RECIST v1.1 or death on study from any cause. The primary efficacy analyses will be performed on all randomized patients as well as on patients with *ESR1* LBD mutations detected in circulating cell-free DNA, with patients allocated to the treatment arm assigned at randomization.

For patients without disease progression or death as of the clinical data cutoff date, their PFS will be censored at the time of last tumor assessment (or censored at the date of randomization, if no tumor assessment was performed after the baseline visit). For patients who start other anti-cancer treatment prior to the documented PFS event, the primary PFS analysis will include

PFS events after other anti-cancer treatment. PFS sensitivity analysis will be performed, censoring PFS on the last tumor assessment prior to starting other anti-cancer therapy.

The two-sided log-rank test stratified by the stratification factors will be used as the primary analysis. The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. Cox proportional hazards models stratified by the stratification factors will be used to estimate a hazard ratio and its 90% confidence interval (CI). The results from the unstratified analysis will also be provided.

Exploratory analysis for PFS may be performed on patient subgroups by demographic disease characteristics.

Determination of Sample Size

The trial is designed to evaluate the clinical activity and safety of GDC-0810 compared with fulvestrant in patients with ER-positive locally advanced or MBC. It is for hypothesis generation, and is not powered to detect minimum clinically meaningful difference between treatment arms.

A total of approximately 152 patients will be enrolled in this study. It is assumed that the median duration of PFS in the fulvestrant control arm is 5.5 months and 8.5 months in the GDC-0810 arm. The final analysis of all randomized patients will be triggered by the occurrence of approximately 95 PFS events, which is expected to occur 26 months after the first patient is randomized. Table 3 shows expected probabilities of observing a hazard ratio of less than 0.5, 0.6 and 0.7 in the final analysis in all randomized patients under varying assumptions for the true underlying hazard ratio. Note that formal hypothesis testing is limited. Rather than testing treatment differences at a statistically significant type I error level of 5%, 90% CI for the hazard ratio will be calculated.

At a target hazard ratio of 0.6, the corresponding 90% CI based on 95 PFS events is (0.43, 0.84) which is considered to provide meaningful precision.

Interim Analyses

The IMC will convene for an interim safety analysis to review unblended summaries of the safety and PK data after the first 20 patients are randomized and have completed two 28-day cycles of therapy.

In addition, after occurrence of approximately 62 PFS events in all patients, the IMC may convene to perform an interim analysis for safety and efficacy. This interim efficacy analysis likely will not be informative for the *ESR1* mutant subset because of the insufficient number of patients with *ESR1* mutant tumors who are projected to have experienced disease progression by that time. The activity of GDC-0810 versus fulvestrant in the *ESR1* mutant subset will be assessed at interim only if a reasonable number of PFS events is available in the subset (for example, 30 PFS events).

Table 4 shows the probability of observing a hazard ratio of less than 0.5, less than 0.6, or 0.7 at interim analysis under varying assumptions of the true underlying hazard ratio for all patients.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AI	aromatase inhibitor
ALT	alanine transaminase
anti-HBc	hepatitis B core antibody
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
BID	bis en die (twice daily)
CBR	clinical benefit rate
CI	confidence interval
CISH	chromogenic in situ hybridization
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMEA	Europe, the Middle East, and Africa
EORTC	European Organization for Research and Cancer
ePRO	electronic patient-reported outcome
ER	estrogen receptor
ER+	estrogen receptor positive

Abbreviation	Definition
E.U.	European Union
^{18}F NaF	F-18 sodium fluoride
FDA	Food and Drug Administration
FES-PET	fluoroestradiol positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hormone receptor
HRQoL	health-related quality of life
ICF	Informed Consent Forms
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IM	intramuscular
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	Institutional Review Board
ISH	in situ hybridization
ITT	intent to treat
IV	intravenous
IWRS	Interactive Web Response System
LBD	ligand-binding domain
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

Abbreviation	Definition
NCI	National Cancer Institute
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic
PO	by mouth; orally
PR	partial response
PRO	patient-reported outcome
QD	once daily
QLQ-BR23	Quality Of Life Questionnaire Breast Cancer Module
QLQ-C30	Quality of Life Questionnaire
qRT-PCR	quantitative real-time PCR
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
SD	stable disease
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
U.S.	United States
VTE	venous thromboembolic event

1. BACKGROUND

1.1 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 therapeutic approach in postmenopausal 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. As such, there is a need for 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 postmenopausal 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- or third-line hormonal treatment after progression on prior hormonal therapy (Di Leo et al. 2010; Baselga et al. 2012). Importantly, there is growing evidence that in the endocrine-resistant state, the 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 *ESR1* affecting the ligand-binding domain (LBD) of the ER-α protein (Segal and Dowsett 2014). In preclinical models, 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 the 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).

1.2 BACKGROUND ON GDC-0810

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.

1.2.1 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.

1.2.2 Summary of Phase I Clinical Data

GDC-0810 is currently being studied in Study GO29642 (formerly known as ARN-810-001), a Phase I*a*/*Ib*/IIa open-label, dose-finding, safety, pharmacokinetic (PK), and proof-of-concept trial of single-agent GDC-0810 *and in combination with palbociclib or luteinizing hormone-releasing hormone (LHRH) agonist* in postmenopausal women with locally advanced or metastatic ER+ breast cancer.

As of 1 October 2014, enrollment in the Phase I dose-escalation portion of Study GO29642 was completed with 41 patients enrolled at doses from 100 mg to 800 mg. Nine dose-escalation cohorts of 3 – 6 patients each were enrolled. Patients received between 100 and 800 mg total daily dose, given once daily (QD) or divided twice daily (BID), with fasting and without fasting. As of *15 April 2016*, a total of *39* patients have discontinued the study: *36* (*88*%) due to disease progression, 1 (2%) due to non-treatment-related cardiac arrest, *1 (2%) due to treatment-related nausea,* and 1 (2%) withdrew consent due to ongoing diarrhea. At the time of the data cutoff (*15 April 2016*), with a median follow-up of *4* months *(range: 1–26 months)*, *16 of 41* (*39*%) patients were on study ≥ 6 months; among those patients previously treated with fulvestrant, 6 of 17 (35%) were on study ≥ 6 months. In addition, robust ER target engagement across all doses was demonstrated by ^{18}F-fluoroestradiol positron emission tomography (FES-PET) scans, and there *were two* confirmed partial response*s* (PR*s*) *as of* the data cutoff.

As of 15 April 2016, 1 of 6 patients had experienced a dose-limiting toxicity (DLT) of Grade 3 diarrhea in the 800-mg 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 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 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 had been enrolled in the combined Phase Ib Cohort D1 and Phase IIa dose-expansion portions 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 GDC-0810 at 600 mg in combination with an 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 GI toxicities from Phase Ia when GDC-0810 was administered under fasting or nonfasting conditions. Safety data for the Phase IIa study remain preliminary with a median treatment duration of 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 the potential risks of GDC-0810, regardless of relatedness to study drug, 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 (VTEs) 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 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.

See the GDC-0810 Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 BACKGROUND ON FULVESTRANT

Fulvestrant belongs to a class of reversible steroidal ER antagonists that directly compete with estrogen for ER binding, and is devoid of the partial agonist properties of tamoxifen. Upon binding to the ER, it blocks estrogen signaling and downregulates the cellular levels of both the ER and progesterone receptor (PgR) (Howell et al. 2000). The affinity of fulvestrant for the ER is approximately 100 fold greater than that of tamoxifen (Howell et al. 2000).

Fulvestrant (250 mg via intramuscular [IM] injection once monthly) was approved by the Food and Drug Administration (FDA) in 2002 and by the European Medicines Agency (EMA) in 2004 (as well as in many other countries) for the treatment of hormone receptor (HR)-positive metastatic breast cancer (MBC) in postmenopausal women with disease progression following anti-estrogen therapy. In multicenter Phase III studies, fulvestrant was found to be at least equivalent to anastrozole (a non-steroidal AI) in the second-line setting (Howell et al. 2002; Osborne et al. 2002). Fulvestrant is also as active as tamoxifen for the first-line treatment of advanced breast cancer (Howell et al. 2004) and displays a level of activity in patients in the post-AI metastatic disease setting similar to that of the non-steroidal AI exemestane (Chia et al. 2008). High-dose fulvestrant (500 mg via IM injection once monthly) has been shown to be associated with significantly longer time to progression for the first-line treatment of women with advanced HR-positive breast cancer compared with anastrozole (Robertson et al. 2009). The 500-mg dose of fulvestrant was recently demonstrated to provide superior progression-free survival (PFS) in women with ER-positive advanced breast cancer than the 250-mg dose (Di Leo et al. 2010). Both doses were well tolerated in these studies and produced fewer estrogenic effects than tamoxifen and less arthralgia than anastrozole (Osborne et al. 2002). These results led to the approval of fulvestrant 500 mg IM on Days 1, 15, 29 and once monthly thereafter as the recommended dose in the United States (U.S.), European Union (E.U.), Canada, Argentina, and Israel as of May 2011 for postmenopausal women with disease progression following anti-estrogen therapy. These studies demonstrate that fulvestrant is an important treatment option for patients with advanced breast cancer and, as such, is considered appropriate control therapy for the present study.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Fulvestrant is an accepted, standard-of-care therapy for the patient population targeted by this study (see Section 4.1.1). In a study of fulvestrant in a population with breast cancer who had previously received endocrine therapy, the most common adverse events reported were injection-site pain (11.6%), nausea (9.7%), and bone pain (9.4%). Fulvestrant should be used with caution in patients with hepatic impairment. Because fulvestrant is administered intramuscularly, it should also be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

GDC-0810 is a potent, orally bioavailable ER-α antagonist that is being developed for the treatment of postmenopausal women with ER+ advanced or MBC whose disease has recurred or progressed following treatment with hormonal therapy. 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 than fulvestrant at clinically relevant exposures. GDC-0810 is currently being tested in a Phase I/IIa study in postmenopausal women with ER+/human epidermal growth factor receptor 2 (HER2)−advanced and MBC.

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 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 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 BID.

At 600 mg by mouth (PO) daily under nonfasting conditions, GDC-0810 *has been well tolerated with most adverse events from Grade 1 to 2 in severity (see Section 1.2.2 for a summary of clinical safety).*

Specific eligibility criteria designed to minimize risk of GI toxicity and other potential risks are included in Section 4.1.2, and robust safety monitoring and risk mitigation strategies for all expected or potential safety risks are described in Section 5.1. The implementation of appropriate dose-modification and treatment guidelines, appropriate choice of inclusion/exclusion criteria, *and* real-time safety monitoring and assessments combine to form the monitoring and risk mitigation system.

In summary, clinical benefit has been observed in patients with refractory breast cancer. The safety profile remains acceptable and is consistent with other established endocrine therapies. The overall risk-benefit ratio of GDC-0810 is considered favorable for the cancer indication.

2. OBJECTIVES

The development of GDC-0810 has been halted and enrollment discontinued; therefore, the primary objectives will not be met.

2.1 EFFICACY OBJECTIVES

The co-primary efficacy objectives for this study are as follows:

- To evaluate the efficacy of GDC-0810 compared with fulvestrant in the intent-to-treat (ITT) population as measured by PFS
- To evaluate the efficacy of GDC-0810 compared with fulvestrant in patients with detectable *ESR1* mutations as measured by PFS

The secondary efficacy objective for this study is as follows:

- To assess the clinical activity of GDC-0810 versus fulvestrant, as measured by objective response rate (ORR), duration of response (DOR), CBR, and overall survival (OS)

2.2 SAFETY OBJECTIVES

The safety objective for this study is as follows:

- To evaluate the safety and tolerability of GDC-0810 compared with fulvestrant, focusing on the nature, frequency, and severity of serious and non-serious adverse events

2.3 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is as follows:

- To assess the pharmacokinetics of GDC-0810 in patients with advanced or MBC resistant to AI therapy

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To estimate the frequency of *ESR1* mutations in patients with advanced or MBC resistant to AI therapy
- To assess the potential relationship between GDC-0810 exposure (as measured by PK variables) and tumor response
- To assess the potential relationship between GDC-0810 exposure (as measured by PK variables) and safety
- To assess disease and treatment-related symptoms, patient function, and health status/health-related quality of life (HRQoL) with GDC-0810 and fulvestrant as measured by the European Organization for Research and Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and its breast cancer module (QLQ-BR23)

- To evaluate patients' treatment satisfaction with medication using a modified version of the Treatment Satisfaction Questionnaire for Medication (TSQM) for use in breast cancer
- To assess whether dynamic (non-inherited) biomarkers, including but not limited to ER/PgR/HER2 expression, luminal A/B status, *PIK3CA* mutations, *AKT1* mutations, *p53* mutations, Ki67 levels, ER target gene expression and PI3K target gene expression, are predictive of response to study treatment, susceptibility to developing adverse events, or progression to a more severe disease state, can provide evidence of treatment activity, or can increase the knowledge and understanding of disease biology
- When post-progression tissue is available, to evaluate the relationship between GDC-0810 exposure and changes in levels of biomarkers, including but not limited to the dynamic (non-inherited) biomarkers described above
- To use whole genome sequencing to assess whether non-dynamic (inherited) polymorphisms in the genome might be predictive of response to study treatment, susceptibility to developing adverse events, or progression to a more severe disease state, or can increase the knowledge and understanding of disease biology
- To explore the role of polymorphisms in drug metabolism enzyme and transporter genes in the pharmacokinetics, safety, and efficacy of GDC-0810 in patients with advanced or MBC, if indicated by PK data

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a multicenter, international, randomized, open-label, Phase II trial with two study arms. A total of approximately 152 patients with advanced or metastatic ER+/HER2− breast cancer who have experienced recurrence or progression of their disease while receiving AI therapy for advanced or metastatic disease or who have relapsed within 6 months after completing adjuvant AI therapy will be enrolled in this study. Patients who are enrolled in Arm A will receive GDC-0810, administered at 600 mg PO daily. Patients who are enrolled in Arm B will receive fulvestrant, administered at 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and Day 1 of each subsequent 28-day cycle thereafter.

A permuted block randomization scheme will be used to ensure an approximate 1:1 allocation of patients who receive GDC-0810 (Arm A) versus patients who receive fulvestrant (Arm B) with respect to two stratification factors per local assessment: geographic region (United States, European Union, and Rest of World) and presence or absence of visceral disease.

Patients may have either measurable disease (per RECIST v1.1) and/or non-measurable, but evaluable, locally advanced or metastatic disease with at least one evaluable bone lesion. Locally advanced disease must not be amenable to resection or

other local therapy with curative intent (see Section 4.1.1 and Section 4.1.2 for detailed inclusion and exclusion criteria).

Patients will receive study treatment in 28-day cycles until documented radiographic disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination. Tumor assessments will be conducted for all patients at screening, *per institutional guidelines, and as clinically indicated.* A schedule of study assessments is provided in Appendix 1 and Appendix 2.

Enrollment in Study GO29689 has been discontinued; therefore, no further patients will be enrolled in this study. Any patient currently enrolled in Study GO28689 experiencing clinical benefit may continue to receive GDC-0810 as a single agent or fulvestrant until disease progression (as assessed by the investigator based on radiographic findings or clinical symptoms), unmanageable toxicity, patient withdrawal of consent, GDC-0810 drug supply has been exhausted, or the Sponsor terminates the study. All patients who are discontinued from study treatment will return for a study drug discontinuation visit within *30* days after the last dose of study treatment and will be followed for adverse events for at least 28 days after the last dose of study treatment.

3.2 END OF STUDY

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

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Patient Population

Female patients with HER2−ER+, locally recurrent, or MBC for which chemotherapy is not indicated will be enrolled in this study. This patient population is usually treated with multiple rounds of single-agent endocrine therapy prior to receiving cytotoxic chemotherapy.

Enrollment in this study is limited to patients who experienced recurrent disease or disease progression while receiving an AI for the treatment of breast cancer or who have relapsed within 6 months after completing adjuvant AI therapy. In addition, these patients may not have received more than one prior chemotherapy regimen or more than two lines of endocrine therapy in the advanced or metastatic disease setting. The requirement for prior treatment with an AI identifies patients who have become resistant to endocrine therapy and would be an appropriate population for fulvestrant therapy. The allowance of up to one prior cytotoxic chemotherapy regimen in the metastatic setting is consistent with prior studies with fulvestrant in a similar patient population. Patients treated with one prior metastatic chemotherapy regimen are not expected to be predisposed to having more severe drug-related toxicities. The inclusion criteria of

Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 – 1 has been selected to test a more homogenous patient population.

Patients will be stratified according to geographic region (United States, European Union, and Rest of World), because potential differences in first- and second-line treatment regimens that are considered local standard-of-care could affect trial outcomes. Patients will also be stratified according to presence or absence of visceral disease, as the presence of visceral disease is a known unfavorable risk factor for ER+ breast cancer that significantly decreases expected survival (Koenders et al. 1992).

3.3.2 GDC-0810 Dose and Schedule

The dose and schedule of GDC-0810 will be 600 mg PO once daily continuously in 28-day cycles, administered under fed conditions (within 30 minutes after eating a meal). In the single-agent Phase Ia study of GDC-0810, only 1 patient out of a total of 6 patients enrolled at the 800-mg, PO, once daily fasting cohort experienced a DLT (Grade 3 diarrhea), which resolved with dose modification and antidiarrheal therapy. However, as additional patients treated with 800 mg PO QD experienced Grade 2 nausea, vomiting, and diarrhea, this dose level was considered intolerable, and thus the MTD of GDC-0810 was not formally determined. As there was a trend for increased exposure and better tolerability under nonfasted conditions, an RP2D of 600 mg QD administered under fed conditions (i.e., within 30 minutes after a meal) was selected based on the overall safety/tolerability and PK/pharmacodynamic (PD) profile of GDC-0810. See the Investigator's Brochure for further details.

3.3.3 Control Treatment

Treatment for ER+, HER2 – breast cancer usually consists of multiple lines of single-agent endocrine therapy, followed by cytotoxic chemotherapy once all endocrine therapy options have been exhausted or symptomatic or rapid disease progression warrants the use of cytotoxic chemotherapy. Fulvestrant has been approved by the U.S. FDA and EMA for the treatment of HR+ or ER+, locally advanced or MBC in postmenopausal women with disease progression following prior anti-estrogen therapy (Howell et al. 2002; Osborne et al. 2002; Di Leo et al. 2010).

The dose and schedule of fulvestrant will be 500 mg via IM injection on Days 1 and 15 of Cycle 1, and Day 1 of each subsequent 28-day cycle thereafter, which is the approved recommended dose and schedule in the United States, European Union, Canada, Argentina, and Israel (as of May 2011).

3.3.4 Open-Label Design

Fulvestrant must be administered via an IM injection, and the two required injections per dose are associated with localized pain and other potential injection-related risks (e.g., bleeding, bruising, infection). Sham injections would result in added risk to patients enrolled on the GDC-0810 arm, and are therefore undesirable. An

acknowledged risk of the open-label design is the potential for bias by patients and investigators that is related to knowledge of the treatment assignment. As a result, all radiographic scans done as part of response assessments will be collected and held centrally and may be reviewed retrospectively to generate an independent response assessment to corroborate the investigator's assessment.

3.3.5 Collection of Archival Tumor Tissue

Archival tissue (or fresh biopsy tissue if archival tissue is not available) will be required from all patients for study entry. If available, both primary and metastatic tissue will be collected. ER+ breast cancer is a heterogeneous disease. Therefore, all patients may not be equally likely to benefit from treatment with GDC-0810. Potential predictive biomarkers (including, but not limited to, the following: expression of Ki67, expression of ER, expression of PgR, *ESR1* mutation status, and alterations in the ER- and PI3K-pathway signaling) will be assessed in tumor samples collected prior to dosing in an effort to identify those patients with ER-driven pathogenesis who are most likely to respond to GDC-0810. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

3.3.6 Optional Collection of Tumor Biopsies at Disease Progression

Understanding the mechanisms of resistance to GDC-0810 is critical for the development of novel agents that target the ER and may provide an opportunity to develop next-generation agents to prevent resistance. If post-progression tumor biopsies can be obtained with minimal risk and discomfort to the patients, it is strongly recommended that tissue be collected from patients who specifically consent to this optional procedure. These tissue samples will be assessed for acquired *ESR1* mutations and alterations in ER- and PI3K-pathway signaling that may help elucidate potential mechanisms of resistance.

3.3.7 Collection of a Blood Sample for Mutation Detection in Tumor DNA

There is increasing evidence that tumor DNA representing the mutational status of tumor cells can be obtained through the isolation of circulating DNA from blood specimens of patients with cancer (Diehl et al. 2008; Maheswaran et al. 2008). Multiple assays are in development to identify mutations in *PIK3CA*, *ESR1,* and PI3K and ER-pathway related genes in circulating tumor DNA (ctDNA). This will be correlated with mutations detected in submitted tumor specimens. Several small retrospective studies have examined the discordance rate between paired samples from the primary tumor and the metastatic biopsy (Dupont Jensen et al. 2011; Gonzalez-Angulo et al. 2011; Sanchez et al. 2011). Loss or gain of *PIK3CA* mutation in metastatic lesions has been observed in up to 33% of patients with MBC (Dupont Jensen et al. 2011). In addition, recent studies have identified mutations in *ESR1* (e.g., ERα) affecting the LBD of the ER (Segal and Dowsett 2014). In nonclinical models, mutant receptors are able to drive ER-dependent transcription and proliferation in the absence of estrogen, suggesting that LBD-mutant forms of the ER are

involved in mediating clinical resistance to endocrine therapy (Li et al. 2013; Robinson et al. 2013; Toy et al. 2013). Identifying potential discordances in the *PIK3CA* and *ESR1* status of the primary and metastatic lesions through the analysis of archival tumor samples and ctDNA, which would represent the most recently collected tissue sample, may help clarify the prognostic and predictive significance of *PIK3CA* and *ESR1* mutations in patients treated with the experimental regimens. This information may also be helpful in the development of a potential companion diagnostic for GDC-0810.

3.3.8 Optional Collection of a Blood Sample for Whole Genome Sequencing

An optional blood sample will also be collected from all patients as a source of normal (germline) DNA for targeted sequencing to determine whether or not sequence variants detected in tumor tissue are somatic mutations or single nucleotide polymorphisms (SNPs).

DNA will also be collected from all patients for next-generation whole genome sequencing. As described above, ER+ breast cancer is a heterogeneous disease; therefore, all patients may not be equally likely to benefit from treatment with GDC-0810. Genomics is increasingly informing our understanding of disease pathobiology and rationale for the development of new therapeutic approaches. Whole genome sequencing provides comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for making these discoveries. Data obtained from whole genome sequencing will also be used to explore whether specific inherited polymorphisms are predictive of response to GDC-0810, susceptibility to developing adverse events, or progression to a more severe disease state.

3.3.9 Pharmacokinetic Evaluation Schedule

PK samples (as outlined in Appendix 3) will be collected in all patients to enable a further understanding of GDC-0810 pharmacokinetics and identification of potential sources of variability influencing GDC-0810 PK. The PK data will also be used to explore potential relationships of exposure (PK variables) to efficacy and safety in the study.

3.3.10 Patient-Reported Outcome Questionnaires

As of protocol amendment version 2, patient reported outcomes questionnaires will no longer be required.

In MBC, the main goals of treatment are to prolong survival and maintain or improve the quality of life (Cardoso et al. 2012). Patient-reported outcome (PRO) measures provide an understanding of a patient's quality of life and the impact of treatment on patients while undergoing therapy. PROs of disease/treatment-related symptoms, function, and global health status will be assessed using the EORTC QLQ-C30 (Appendix 4) in conjunction with the QLQ-BR23 breast cancer module (Appendix 5). The EORTC QLQ-C30 and its breast cancer–specific module, the QLQ-BR23, are validated and

reliable self-report measures (Aaronson et al.1993; Sprangers et al. 1996; Osoba et al. 1997).

The modified version of the TSQM (Appendix 6) is a validated and reliable self-report questionnaire that assesses overall patient satisfaction with their study treatment (Atkinson et al. 2004). The modified version of the TSQM was tailored and approved for use in breast cancer patients.

3.3.11 DNA for Exploratory Pharmacogenetic Polymorphisms

Blood samples will be used for the evaluation of genetic polymorphisms of drug metabolic enzymes (including, but not limited to CYP2C9, CYP3A4/5, and UGT1A1) and transporters (e.g., OATP1B1) and genetic variants that could contribute to potential safety and efficacy concerns. For sample handling procedures, storage conditions, and shipment instructions, see the laboratory manual. Only in circumstances where there is concern for the collection of this genetic material for the above evaluations can this assessment be considered not mandatory as part of study assessments in this study. Results of any analyses from these samples will be reported outside the clinical study report.

It is established that genetic variants of drug-metabolizing enzymes and transporters can affect the pharmacokinetics of drugs, which affect 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 a higher risk for adverse effects associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006). Although in vitro studies can help elucidate the roles of enzymes in the metabolism of the drug, these results are not always predictive of in vivo metabolism for a number of reasons, such as differences in drug concentrations that the enzymes encounter in vitro and in vivo. For this reason, a blood sample for DNA isolation is to be collected from all patients dosed with GDC-0810 in this study for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics, safety, or response to GDC-0810. The decision to analyze the samples will be based on a review of the pharmacokinetics and response data.

3.4 OUTCOME MEASURES

3.4.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study, for all patients as well as the subset of patients with *ESR1* mutations, is as follows:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator per RECIST v1.1 (See Appendix 7) or death from any cause on study, whichever occurs first

3.4.2 Secondary Efficacy Outcome Measures

The secondary outcome measures for this study are the following:

- OS, defined as the time from randomization to the time of death from any cause
- Objective response (PR plus complete response [CR]) as determined by the investigator per RECIST v1.1 (see Appendix 7)
- DOR, defined as the time from the first occurrence of a documented objective response until first observation of disease progression, as determined by the investigator per RECIST v1.1 (see Appendix 7), or death from any cause on study, whichever occurs first
- Clinical benefit, defined as PR, CR, or stable disease (SD), lasting for at least 24 weeks from the time of randomization

3.4.3 Safety Outcome Measures

The safety and tolerability of GDC-0810 will be assessed using the following:

- The incidence, nature, and severity of adverse events reported during the adverse event reporting period (see Section 5.3.1), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE, v4.0)
- Incidence, nature and severity of serious adverse events
- Incidence of adverse events leading to study treatment discontinuation, modification or interruption
- Clinically significant changes in vital signs, physical findings, and clinical laboratory results during and following GDC-0810 or fulvestrant administration during the adverse-event reporting period

3.4.4 Pharmacokinetic Outcome Measures

Sparse PK samples will be collected as outlined in Appendix 3 and *may* be analyzed using population PK methods to estimate apparent clearance, volume of distribution, absorption rate constant, and other appropriate measures as data allow*, and plasma concentrations will be summarized by visit*. Please refer to Section 6.6 for additional information.

3.4.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Assessment of RNA in pre- and post-treatment tumor specimens, including assessment of PI3K and ER target gene expression signatures, ER, PgR, and HER2 status and luminal A/B status
- Alterations of DNA in pre- and post-treatment tumor specimens, including *ESR1* mutations, *PIK3CA* mutations, *AKT1* mutations, and *TP53* mutations
- Assessment of Ki67 levels in pre- and post-treatment tumor specimens

- Alterations in ctDNA from peripheral blood, including but not limited to *ESR1*, *PIK3CA* and *AKT1*
- Assessment of mean change in disease/treatment-related symptoms, function and health status/HRQoL scales of the EORTC QLQ-C30 (Appendix 4) and the EORTC QLQ-BR23 breast module (Appendix 5)
- Assessment of mean treatment satisfaction on the subscales (side effects, convenience, and global satisfaction) of a modified version of the TSQM (Appendix 6)
- Whole genome sequencing data will be analyzed in the context of this study and explored in aggregate with other studies to better understand disease pathobiology and guide the development of new therapeutic approaches. Given the complexity and exploratory nature of these analyses, whole genome sequencing data and analyses will not be shared with investigators or study participants unless required by law.

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with ER+ HER2−, locally advanced or MBC will be enrolled in the study.

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria for study entry:

Disease-Specific Inclusion Criteria

- Postmenopausal women with histologically or cytologically confirmed invasive, ER+/HER2− (defined by local guidelines) metastatic or inoperable (not amenable to resection or other local therapy with curative intent), locally advanced breast cancer

  Postmenopausal is defined as meeting at least one of the following criteria:

  – Prior bilateral oophorectomy

  – Age ≥ 56 years and 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 after 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 after medical menopause on luteinizing LHRH agonist (on stable dose ≥ 1 year), with amenorrhea ≥ 1 year since last menses and serum estradiol levels (< 20 pg/mL) in the postmenopausal range irrespective of FSH/LH levels

  - Women with therapy-induced amenorrhea must agree to remain abstinent or use single or combined non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of GDC-0810 or at least $1\ year$ after the last dose of fulvestrant. Abstinence is only acceptable if it is in line with 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.
  - Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.
- Patients for whom endocrine therapy (e.g., fulvestrant) is recommended and treatment with cytotoxic chemotherapy is not indicated at time of entry into the study, as per national or local treatment guidelines
- Radiologic/objective evidence of recurrence or progression to the most recent systemic therapy for breast cancer
- Radiologic/objective evidence of breast cancer recurrence or progression while on or within 6 months after the end of adjuvant treatment with an AI, or progression while on or within 1 month after the end of prior AI treatment for locally advanced or MBC. The AI (letrozole, anastrozole, or exemestane) does not have to be the most recent treatment before randomization, but patients must have received at least 4 weeks of treatment with an AI.
- Patients must have measurable disease by RECIST v1.1 or non-measurable, evaluable disease with at least one evaluable bone lesion by RECIST v1.1 based on radiologic scans within 28 days of Day 1 of Cycle 1. Bone lesions that have been irradiated are not evaluable.

General Inclusion Criteria

- Signed Informed Consent Form
- Age ≥ 18 years
- ECOG Performance Status of 0 or 1 (see Appendix 8)
- Consent to the collection of a formalin-fixed paraffin-embedded (FFPE) block or a minimum of 10 freshly cut unstained tumor slides (submission of 15–20 is strongly encouraged) from archival tumor tissue or a newly collected (“fresh”) tumor sample for protocol-mandated exploratory assessments
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 days prior to Day 1 of Cycle 1:
  - Absolute neutrophil count ≥ 1500/μL
  - Platelet count ≥ 90,000/μL

- Hemoglobin ≥ 9.0 g/dL (90 g/L)
- Albumin ≥ 3.0 g/dL (30 μmol/L)
- Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
- Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) ≤ 1.5 × ULN, with the following exceptions:

  Patients with documented liver metastases: AST and/or ALT ≤ 5.0 × ULN

  Patients with documented bone metastases: ALP ≤ 5.0 × ULN

  Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min based on Cockroft–Gault glomerular filtration rate (GFR) estimation

  $$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine})}$$

  International normalized ratio (INR) < 1.5 and activated partial thromboplastin time (aPTT) < 1.5 × ULN; for patients requiring therapeutic anticoagulation therapy, a stable INR ≤ 2.5

4.1.2 Exclusion Criteria

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

Disease-Specific Exclusion Criteria

- HER2-positive disease (immunohistochemistry [IHC] 3+ staining, fluorescence in situ hybridization [FISH] positive, and/or chromogenic in situ hybridization [CISH] positive)
- Prior treatment with fulvestrant
- Prior anti-cancer therapy within 2 weeks prior to Cycle 1 Day 1
- Prior radiation therapy within 2 weeks prior to Cycle 1 Day 1
- Prior treatment with > 1 cytotoxic chemotherapy regimens or > 2 endocrine therapies for advanced or metastatic disease
- Ongoing, acute treatment-related toxicity that has not resolved to Grade ≤ 1 or been deemed stable by the investigator
- Concurrent hormone replacement therapy
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy; use of bisphosphonate therapy or denosumab for other reasons (e.g., bone metastasis, osteoporosis, etc.) is allowed (see Section 4.4.1).
- Known untreated or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control); a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will be performed at screening if required by the local health authority

  Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:

  - Evaluable or measurable disease outside the CNS is present.
  - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - Screening CNS radiographic study is ≥ 8 weeks since completion of radiotherapy and ≥ 4 weeks since the discontinuation of corticosteroids
- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence; patients with slow-growing, benign tumors are allowed

General Exclusion Criteria

- Inability or unwillingness to swallow pills or receive IM injections
- History of malabsorption syndrome, short bowel syndrome, gastric resection, or other condition that would interfere with enteral absorption
- History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)
- Active bowel inflammation (e.g., diverticulitis)
- History of endometrial cancer or atypical endometrial hyperplasia
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or current known active infection with hepatitis B virus (HBV), or hepatitis C virus (HCV)

  Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [anti-HBc]) or hepatitis C (HCV antibody). Unless required by local regulations, patients are not required to have HIV, HBV, or HCV assessments at screening if these assessments have not been previously performed.
  - Patients who are positive for anti-HBc are eligible only if testing is also positive for hepatitis B surface antibody and polymerase chain reaction (PCR) is negative for HBV DNA.
  - Patients who are positive for HCV serology are eligible only if testing for HCV RNA is negative.
- Active autoimmune disease that is not controlled for at least 6 months by stable doses of nonsteroidal or steroidal (< 10 mg of prednisone per day) anti-inflammatory drugs or active inflammatory disease, including small or large intestine inflammation such as Crohn's disease or ulcerative colitis, which requires immunosuppressive therapy
- Clinically significant cardiac or pulmonary dysfunction, including the following:
  - Current uncontrolled Grade ≥ 2 hypertension or unstable angina

  - Symptomatic congestive heart failure of New York Heart Association Class II, III or IV
  - Serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia or conduction abnormality that has been treated and for which the patient is no longer at risk for serious arrhythmia (e.g., Wolff-Parkinson-White syndrome treated with surgical ablation)
  - History of acute coronary syndrome or unstable angina within 6 months prior to Cycle 1, Day 1
- History of congenital long QT syndrome or corrected QT interval (QTcF) $>$ 470 msec
- Immunocompromised status due to current known active infection with HIV or due to the use of immunosuppressive therapies for other conditions
- Need for current chronic corticosteroid therapy ($\geq$ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)

  Inhaled corticosteroids are allowed
- Pregnancy, lactation, or breastfeeding
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
- Major surgical procedure or significant traumatic injury within 28 days prior to Day 1 of Cycle 1 or anticipation of the need for major surgery during the course of study treatment
- Inability, in the opinion of the investigator, to comply with study and follow-up procedures

4.2 METHOD OF TREATMENT ASSIGNMENT

After written informed consent has been obtained and eligibility has been established and approved, the study site will obtain the patient's identification number and treatment assignment from the Interactive Web Response System (IWRS). Patients will be randomized to receive either GDC-0810 or fulvestrant in an approximate 1:1 ratio through the use of a permuted block randomization method.

Randomization will be stratified by the following criteria:

- Visceral versus non-visceral disease:
  - Visceral disease: metastatic disease in the lung, liver, adrenal glands, brain, heart, pericardium, pleura, peritoneum, or other organs of the chest, abdomen and pelvis
  - Non-visceral disease: absence of metastatic disease in visceral organs. Pleural effusions and/or ascites. Disease involving lymph nodes and disease involving bone are not considered to be visceral disease.

- Geographical region:
  - United States
  - European Union
  - Rest of World (remaining countries)

The Sponsor, the investigators, and the patients will be unblinded to treatment assignment.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 GDC-0810

GDC-0810 will be supplied by the Sponsor as white oblong tablets containing 200 mg GDC-0810 free acid packaged in 30-ct, 60cc high-density polyethylene bottles with child-resistant closures and tamper-proof heat induction seals. The drug product container includes a desiccant packet. Each bottle of study drug will be labeled with the lot number, the Sponsor's name, and directions for patient use and storage.

For further information on the formulation and handling of GDC-0810, see the pharmacy manual and the GDC-0810 Investigator's Brochure.

4.3.1.2 Fulvestrant

Fulvestrant will be obtained by the site and provided as standard of care therapy, except where it is required by local regulations to be supplied by the Sponsor. For countries in which the Sponsor is supplying fulvestrant, it will be supplied in sterile single-patient, prefilled syringes containing 50 mg/mL fulvestrant, as a 5-mL injection. For details regarding the storage of fulvestrant, please refer to the fulvestrant package insert or local prescribing information.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 GDC-0810

GDC-0810 is intended for oral administration. The 600-mg dose of GDC-0810 will be taken orally once per day until disease progression or intolerable toxicity. GDC-0810 is supplied as 200-mg tablets; therefore, patients will take three 200-mg tablets daily to receive a 600-mg dose. Each 600-mg dose should be taken within 30 minutes after a meal, and efforts should be made by patients to take the dose at the same approximate time each day. If a dose is missed (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

On clinic visit days that require a predose blood draw for PK sampling and/or laboratory assessments (see Appendix 1 and Appendix 2), patients will be instructed to take their morning, oral study-treatment dose in the clinic after the completion of the pre-treatment

assessments. For all other days, the daily study treatment dose should be taken at home.

A sufficient number of GDC-0810 tablets should be provided to the patient to last until the next visit. Patients will be instructed to bring their bottles of study drug and their medication diary with them to each study visit.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Fulvestrant

Fulvestrant 500 mg will be administered in the clinic as two IM injections of 250 mg each on Days 1 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle until disease progression or intolerable toxicity. For more details regarding the dosing instructions and safety profile of fulvestrant, please refer to the fulvestrant (Faslodex®) Package Insert or Summary of Product Characteristics (SmPC).

The fulvestrant dose level cannot be modified. Guidelines for dosage modification and treatment interruption or discontinuation of fulvestrant are provided in Section 5.1.5.1.

Any overdose or incorrect administration of fulvestrant should be noted on the Fulvestrant Administration eCRF. Adverse events associated with an overdose or incorrect administration of fulvestrant should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (GDC-0810 and fulvestrant) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 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 his or 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 ER+ breast cancer
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for ER+ breast cancer
- Provision of study drug is not permitted under the laws and regulations of the patient's country

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

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients treated with anti-seizure medications should have levels monitored regularly.

Palliative and supportive care for disease-related symptoms may be administered at the investigator's discretion. Patients who experience toxicities should have their symptoms treated as clinically indicated. Anti-emetics and anti-diarrheal medications should not be

administered prophylactically before initial treatment with study drug. At the discretion of the investigator, prophylactic anti-emetic and/or anti-diarrheal medication(s) may be used as per standard clinical practice before subsequent doses of study drug.

Pain medications administered per standard clinical practice are allowed. Bone-sparing agents (e.g., bisphosphonates, denosumab) for palliation of bone metastases or for the treatment of osteoporosis/osteopenia are allowed, but initiation of such agents or modification of the pre-study bisphosphonate or denosumab treatment regimen require the approval of the Medical Monitor and should be avoided where possible.

GDC-0810 was shown to inhibit human CYP2B6 and CYP2C enzymes in vitro; therefore, drug-drug interactions with co-administered CYP2B6 and CYP2C substrates cannot be excluded and should be avoided where possible. Note that many of these medications are also metabolized by other CYP enzymes which are not inhibited by GDC-0810 (e.g., CYP3A4), thus attenuating the potential for drug-drug interactions to some extent. If there is clinical need for a particular CYP2B6 or CYP2C substrate drug, dose adjustments and/or use of alternative medications are recommended.

A list of possible CYP2B6 and CYP2C substrates can be found in Appendix 9.

4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited for at least 14 days prior to Cycle 1 Day 1 dosing and during the study treatment:

- Therapy intended for the treatment of cancer (regulatory-approved or experimental), including chemotherapy, radiation therapy, immunotherapy, biologic therapy, herbal therapy, radiopharmaceutical therapy, or endocrine therapy.

  Local radiotherapy is not permitted. It is understood that there may be extreme circumstances requiring local radiotherapy in which the investigator does not believe that the symptoms are a result of disease progression (e.g., impending fracture), and the radiation field does not encompass a target/non-target lesion. In such cases, the investigator must obtain approval from the Medical Monitor, and such patients should have a tumor assessment of the lesion(s) before they actually receive the radiotherapy. If a patient received radiation therapy and a target or non-target lesion is included in the field of radiation, the lesion(s) will become unevaluable for tumor response.

  Further reasons for avoiding local radiotherapy include the difficulty in distinguishing new symptomatic pain or worsening of lytic bone lesions from disease progression. Radiation therapy to a specific site renders that lesion unevaluable for tumor response. Previous clinical experience also suggests that new bone pain is frequently a symptom of disease progression. Bone pain secondary to study treatment can be treated with pain medications, nonsteroidal anti-inflammatory drugs, or corticosteroids.

Use of the following concomitant therapies is prohibited for at least 7 days prior to Cycle 1 Day 1 dosing and during the study treatment:

- Hematopoietic growth factors (e.g., erythropoietins, G-CSF, and GM-CSF) are not to be administered prophylactically. Use of these agents should be reserved for cases of severe neutropenia and anemia per the labeling of these agents and require the approval of the Medical Monitor.
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective ER modulators (e.g., raloxifene) are prohibited.
- Owing to their narrow therapeutic index and the potential for drug-drug interactions, concomitant therapy with warfarin or phenytoin is prohibited. Please see Appendix 9 for further information.

4.5 STUDY ASSESSMENTS

Please see Appendix 1, Appendix 2, and Appendix 3 for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases that have occurred within the previous 5 years before Cycle 1 Day 1, surgeries, breast cancer history (including tumor characteristics such as HR status, location of metastases, prior cancer therapies, surgeries and procedures), menopausal status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity in accordance with the applicable laws (e.g., health authority requirements).

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems, as well as measurements of weight and

height (height is measured at screening only). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

An assessment of the patient's ECOG Performance Status (see Appendix 8) will be completed at screening and as specified in the Schedule of Assessments (see Appendix 1 and Appendix 2).

At subsequent visits (or as clinically indicated), symptom-directed physical examinations should be performed. Particular attention should be given to symptoms related to adverse events of special interest (e.g., diarrhea). Detailed information about any diarrhea symptoms (e.g., urgency, loss of stool continence, impact on lifestyle) as well as management (e.g., dietary changes, fluids, probiotics, use of anti-diarrheals) should be assessed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs, collected at screening*, per institutional guidelines, and as clinically indicated* and at each subsequent visit, will include measurements of heart rate, systolic and diastolic blood pressure (while the patient is in a seated position), and oral or tympanic temperature.

4.5.5 Tumor and Response Evaluations

Tumor assessments will be performed at screening, *per institutional guidelines*, and when clinically indicated. All known measurable sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. A documented standard-of-care tumor assessment performed within 28 days before Cycle 1 Day 1 may be used for the screening assessment, provided it meets the requirements described below.

Response assessments will be performed by the investigator, on the basis of physical examinations and imaging scans (Appendix 7).

CT scans are the preferred imaging modality for tumor assessments. Tumor assessments should include a diagnostic quality, contrast-enhanced CT scan of the chest, abdomen, and pelvis at baseline. CT scans of the neck should be included if clinically indicated. A CT for tumor assessment may be acquired on a PET/CT scanner if it is of full diagnostic quality and includes intravenous (IV) contrast.

In patients for whom a CT scan is contraindicated due to a CT IV contrast allergy, a CT of the chest without contrast and MRI of the abdomen and pelvis with contrast are recommended. MRI of the chest may only be performed with the approval of the Sponsor. In these patients, at screening, tumor assessments should include a

diagnostic quality, contrast-enhanced MRI scan of the chest (if approved), abdomen, and pelvis. MRI scans of the neck should be included if clinically indicated.

The same imaging method used at screening must be used throughout the study.

To be suitable for RECIST assessments, CT/MRI scans should ideally have a maximum thickness of 5 mm and minimal gaps. Subsequent tumor assessments should include CT/MRI scans of the chest*, pelvis,* and abdomen and other known sites of disease. In addition to the scheduled on-protocol CT/MRI scans, CT/MRI scans may be repeated at the investigator's discretion at any time if progressive disease is suspected.

A technetium bone scan should be performed at screening (up to 28 days prior to Cycle 1 Day 1) to evaluate for the presence of bone metastases. Positive areas on bone scans should be evaluated by X-ray, CT scan, or MRI prior to randomization (up to 28 days prior to Cycle 1 Day 1). Bone scans should be repeated in the event of clinical suspicion of progression of existing bone lesions, the development of new bone lesions, and in the assessment of a CR, if any disease was evident at screening. For adequate assessment of bone lesions, it is expected that the radiologist will adjust window leveling accordingly.

To ensure a valid comparison of tumor data and uniformity in the assessment of tumor response during the study, the following procedures must be implemented at the study site:

- All lesions identified at baseline (target and non-target) will be reassessed using the same method throughout the course of the study.
- All CT scans and MRIs obtained for all patients enrolled at the center should be reviewed by the local radiologist who, together with the investigator, will determine the local assessment of response and progression. All bone scans obtained from the patients with bone metastases should be reviewed similarly.
- All radiological data (CT scan, MRI and bone scan, etc.) and photos for skin lesions obtained at baseline, during treatment period and the follow-up period must be sent to a central imaging vendor contracted by the Sponsor within 2 weeks of imaging.
- Tumor response and progression will be assessed and will be the basis for the efficacy analyses (along with survival information). The main analysis of the trial will be based on the local radiology review results.

Patients who discontinue study treatment for any reason other than disease progression will continue to undergo tumor response evaluations until progressive disease or initiation of other anti-cancer therapy.

4.5.5.1 Response Evaluations in Patients with Bone-Only Disease

For patients with bone-only disease not visible on the CT or MRI scans being performed as part of the tumor assessments, a bone scan should be repeated at every tumor assessment ($\pm$7 days for flexibility in the event of isotope shortage), and when clinically

indicated. Abnormalities found on subsequent bone scans should be evaluated by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. In the absence of measurable disease at baseline, the following will be considered progression among patients with lytic or mixed (lytic+sclerotic) bone lesions:

- The appearance of one or more new lytic lesions in bone
- The appearance of one or more new lesions outside of bone
- Unequivocal progression of existing bone lesions

Pathologic fracture, new compression fracture, or bone metastasis complications will not be considered as evidence of disease progression unless one of the above-mentioned criteria is also fulfilled.

Patients with symptoms of rapidly progressing disease without radiological (or photographical) evidence will not be considered to have progressed for efficacy analyses. For patients with bone-only disease, response will be determined *based on radiographic findings or clinical symptoms* (Appendix 7) with the following extension: the overall lesion response at each assessment will be based solely on non-target lesion responses. Specifically, in the absence of new lesions, the overall lesion response at each assessment will be one of the following: CR, SD, unknown (i.e., missing data), or *progressive disease*. All assessments not qualifying for CR, progressive disease, or unknown would be classified as SD. In the presence of any new lesions, the overall lesion response will be progressive disease.

If a patient presents with both irradiated and non-irradiated bone lesions, only the non-irradiated lesions should be followed for tumor assessments unless progression is documented after radiation.

In the event that it is not feasible to perform a bone scan, or it is anticipated that it will not be feasible to perform bone scans throughout the study, F-18 sodium fluoride (^{18}F NaF) PET scans may be substituted. In this case, an ^{18}F NaF PET scan must be performed at screening and, in patients with bone-only disease not visible on the CT or MRI scans being performed as part of the tumor assessments, must be repeated at every tumor assessment.

4.5.6 Endometrial Thickness Assessment

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

4.5.7 Electrocardiograms

An electrocardiogram (ECG; 12-lead) is required at screening and at the study drug discontinuation visit, and may be repeated during the study as clinically indicated.

All ECG recordings should be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. An unscheduled PK sample should be obtained, and the Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. A decision on study drug discontinuation should be made, as described in Section 5.1.5. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

Clinically significant abnormalities observed during screening will be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities and/or QTcF prolongations that meet the criteria described above will be recorded on the Adverse Event eCRF.

4.5.8 Patient-Reported Outcomes

With the initiation of protocol amendment version 2, patient-reported outcomes will no longer be collected.

The EORTC QLQ-C30, QLQ-BR23, and a modified version of the TSQM will be collected to more fully characterize the clinical profile of GDC-0810 and fulvestrant.

The EORTC QLQ-C30 (see Appendix 4) and the QLQ-BR23 (see Appendix 5) are validated and reliable self-report measures (Aaronson et al. 1993; Sprangers et al. 1996; Osoba et al. 1997). The EORTC QLQ-C30 (version 3) consists of 30 questions that assess the following: global health status/HRQoL, five aspects of patient functioning (physical, emotional, role, cognitive, and social); three symptom scales (fatigue, nausea and vomiting, and pain); and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of “the last week.” The EORTC QLQ-BR23 breast cancer module also uses a recall period of “the past

week," and consists of 23 additional items assessing disease/treatment symptoms (systemic therapy side effects, breast symptoms, arm symptoms, and hair loss) and aspects of patient functioning (body image, sexual functioning, and future perspective).

The modified version of the TSQM (see Appendix 6) is a validated instrument consisting of 11 questions that measure patients' satisfaction with medication. The 11 items incorporate 3 domains: side effects, convenience, and global satisfaction. The original version of the TSQM also contains a three-item subscale of effectiveness of treatment. The original TSQM had not previously been used in a cancer population, and during a validation study, cancer patients clearly indicated that they were not able to interpret or respond to the items on the effectiveness subscale.

The PRO instruments will be translated as required in the local language and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires scheduled for administration during a clinic visit must be completed by the patient at the investigational site at the start of the clinic visit prior to other study assessments and before administration of study treatment. Interviewer assessment is allowed, but can only be conducted by a member of the clinic staff, if the patient is unable to complete the measure on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

An electronic PRO (ePRO) data collection modality will be employed. To capture PRO data during study treatment, patients will complete the questionnaires on a validated ePRO tablet at the site. The ePRO device and instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via a pre-specified transmission method (e.g., Web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be accessed securely by appropriate study personnel via the Internet.

Please see Appendix 1 for the schedule of PRO assessments. It should take approximately 10 minutes to complete the PRO assessments at each timepoint.

4.5.9 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis (see Appendix 1 and Appendix 2 for the collection schedule):

- Hematology: red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, and monocytes), and platelet count

  Reporting the differential as absolute counts is preferred, but percent is accepted
- Coagulation: aPTT and INR

- Serum or plasma chemistry: glucose, blood urea nitrogen or urea, creatinine, sodium, potassium, chloride, magnesium, bicarbonate, calcium, total protein, albumin, total bilirubin, ALP, AST, and ALT
- Urinalysis (macro): specific gravity, pH, glucose, protein, ketones, and blood, with reflex microscopic analysis done if macro is abnormal

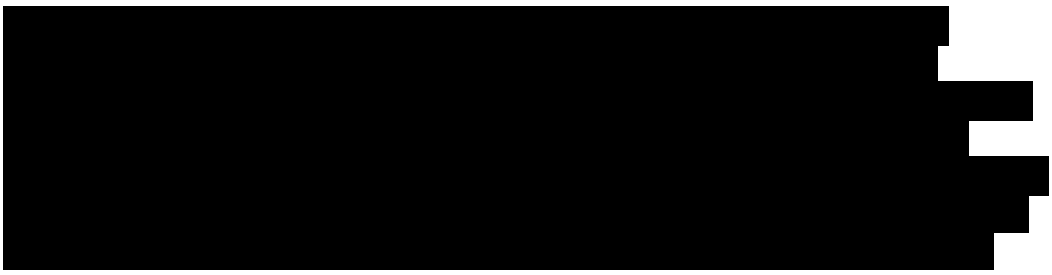
Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis (see Appendix 1, Appendix 2, and Appendix 3 for the collection schedule):

- Plasma samples for ctDNA isolation for exploratory research on candidate biomarkers, including but not limited to the following: *ESR1* mutations, *PIK3CA* mutations, and *AKT1* mutations
- Plasma sample to be banked for potential, future blood-based companion diagnostic development
- Plasma samples for PK analysis
- Blood for pharmacogenetic assessment (where approved by local regulatory authorities)
- Archival or newly collected (fresh) tumor tissue samples for *DNA and/or RNA extraction for* exploratory *NGS or other* research on candidate biomarkers, including but not limited to the following: *ESR1* mutation status, *PIK3CA* mutation status, ER/PgR and HER2 expression, LumA/B subtype, Ki67 IHC assay, and other assessments related to ER and PI3K signaling pathways

  Sites must confirm the availability of a representative FFPE tumor specimen before initiating screening procedures.

  In the event that multiple tissue blocks are available for a given patient (e.g., primary tumor and metastatic site), the most recently collected tumor sample must be submitted; both primary and metastatic tissue should be submitted where possible.

  Tumor blocks are preferred, but in the event that local regulations prevent the shipment of tumor blocks, 10 unstained, serially cut, 5-μM thick slides are requested (15 – 20 slides are preferred). Minimum tissue requirements are further described in the laboratory manual. Cytological, fine-needle aspiration, and bone biopsy samples are not acceptable.



[redacted]

- If available, fresh tumor tissue samples collected at the time of disease progression

  Tissue collection at the time of disease progression is not required for study participation. The tissue specimen will be requested for those patients who sign the Optional Research Informed Consent, and will be used for *DNA and/or RNA extraction for* exploratory research on mechanisms of resistance, including but not limited to the following: *ESR1* mutation status, *PIK3CA* mutation status, and other assessments related to ER and PI3K signaling pathways.

- Optional blood sample for whole genome sequencing using an appropriate next-generation sequencing (NGS) platform

Laboratory manuals and supply kits will be provided for all central laboratory assessments. For detailed sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4.

4.5.10 Assay Methods

4.5.10.1 Mutational Analysis for *ESR1*

Somatic mutations in the LBD of the *ESR1* gene confer ligand independence and are found in approximately 40% of metastatic breast cancers but are rare in primary breast cancers. ctDNA obtained from plasma offers a robust mutation detection alternative to tissue that can be collected with less inconvenience and risk to patients, particularly those with bone metastases that are difficult to biopsy. Quantitative real-time PCR (qRT-PCR) assays or NGS assays designed to interrogate the LBD of *ESR1* offer a sensitive and quantitative method to detect mutations from ctDNA. DNA will be extracted from plasma samples and subjected to NGS and/or qRT-PCR assays that detect the wild-type allele, as well as mutations that include, but are not limited to, the following amino acid changes: D538(G), Y537(S, N, C), E380(Q), L536(Q, H, P, R), S463P and P535H. Assays may also be run on metastatic tumor tissue if such tissue is available. Assays from all samples will be run in a central laboratory on analytically validated NGS and/or qRT-PCR platforms, and mutation calls will be made using appropriate cutoffs and automated software. The information about the spectrum and the prevalence of *ESR1* mutations may help with the development of a companion diagnostic for GDC-0810.

4.5.10.2 ER, PgR, and HER2 Analysis

PgR, ER, and HER2 status will be determined at a central laboratory using standardized immunohistochemical and/or FISH procedures, or will be determined using an analogous RNA-based method.

4.5.10.3 Circulating Tumor DNA Analysis

ctDNA will be extracted from plasma samples collected from patients and used for the detection of oncogenic mutations and DNA methylation using appropriate technologies. The prevalence of the mutations measured at baseline and after treatment may provide information on response or resistance to therapy.

4.5.10.4 Messenger RNA Expression Profiling

In cases where there is sufficient archival tissue to isolate RNA, gene expression may be performed using gene expression assays conducted using appropriate technologies. Analysis may include, but is not limited to, a panel of genes that is important for intrinsic subtyping, breast cancer biology, and immune-related and ER signaling. The goal will be to generate a database of expression status to examine whether there are gene expression patterns associated with clinical response to GDC-0810.

4.5.10.5 Tumor Somatic Mutation Analysis

In cases where there is sufficient material to isolate DNA, NGS may be performed using an appropriate NGS platform, such as Illumina or an equivalent. The goal will be to determine whether the somatic mutations are associated with clinical response to GDC-0810.

4.5.10.6 Copy Number Analysis

The level of copy number alterations in cancer-related genes may be determined using DNA-based technologies, either cytogenetically, using chromosomal in situ hybridization (ISH), NGS platforms, reverse transcription-PCR–based platforms or by using equivalent technologies. For cytogenetic assays, detection may be either fluorescence-based (FISH assay) or chromogenic-based (CISH). Data on the increased copy number of ER- or PI3K pathway–activating genes may provide information on response or resistance to therapy.

4.5.10.7 Plasma Biomarker Analyses

Assays that assess the expression of soluble, systemic cytokines, and chemokines from the plasma of patients will be completed using appropriate methodologies, such as ELISA-based, mass spectrometry-based, or equivalent technologies.

4.5.10.8 Plasma Pharmacokinetic Samples

Plasma concentrations of GDC-0810 will be measured in a designated bioanalytical laboratory using a validated liquid chromatography tandem mass spectrometry assay. Plasma samples may be used for the exploratory evaluation of safety and/or response biomarkers, the identification and profiling of potential GDC-0810-related metabolites, ex-vivo protein binding and/or PK or PD assay development purposes.

4.5.10.9 Pharmacogenetic Polymorphism Assay

If approved by the local regulatory authority, pharmacogenetic polymorphisms will be assayed using multiplex PCR, allele-specific PCR, direct sequencing, or other acceptable methods. Results may be correlated to GDC-0810 exposure or other clinical

measures to better understand the impact of genetic variants on drug metabolism, exposure, adverse events, and/or response.

A blood sample will also be utilized as a source of normal DNA to determine whether sequence variants in the *ESR1* gene and in other relevant oncogenes in the tumor DNA are somatic mutations or SNPs.

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4.

4.5.10.10 Sample for Whole Genome Sequencing

A single blood sample will be collected for whole genome sequencing from patients who consent to this optional assessment, and may be sent to one or more laboratories for analysis using an appropriate NGS platform. Whole genome sequencing data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health-research databases for broad sharing with other researchers. Study participants will not be identified by name or any other personally identifying information.

4.5.11 Timing of Study Assessments

4.5.11.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. ICFs for patients who are not subsequently enrolled will be maintained at the study site.

Screening and pretreatment tests and evaluations will be performed within 28 days preceding Cycle 1, Day 1 (defined as the day of the first dose of study drug), unless otherwise specified. Tests that are performed as standard of care before obtaining informed consent may be used for screening and baseline assessments, provided that they have been performed within this timeframe. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first administration of study drug.

4.5.11.2 Assessments during Treatment

All assessments will be performed per institutional guidelines or as clinically indicated, unless otherwise noted. On treatment days, assessments should be performed before study drug administration unless otherwise noted. *When laboratory assessments are performed, r*esults of local laboratory assessments must be reviewed, and the review documented, before study drug administration.

If a visit is scheduled on a holiday that precludes a protocol-specified procedure, the procedure should be performed on the nearest following date. Subsequent protocol-specified procedures should remain synchronized with Day 1 of the most recent cycle, unless otherwise noted.

Refer to the Study Flowchart provided in Appendix 1 and Appendix 2 for the schedule of treatment period assessments.

4.5.11.3 Study Drug Discontinuation Visit

All patients who are discontinued from study drug will return for a study drug discontinuation visit within 30 days after the last dose of study treatment. The treatment completion visit procedures and assessments should be performed after permanent discontinuation of study drug. The visit at which disease progression is recorded may serve as the study drug discontinuation visit, provided that all tests required at the study drug discontinuation visit are performed. Assessment of disease progression based on clinical examination must be confirmed by radiographic assessment prior to or at the study drug discontinuation visit and before initiating new anti-cancer therapy.

Refer to the Study Flowchart in Appendix 1 and Appendix 2 for the schedule of assessments to be performed at the study drug discontinuation visit.

4.5.11.4 Follow-Up Assessments

All patients will be followed for safety for at least 28 days after the last administration of study therapy. Ongoing adverse events related to study treatment will be followed until the event has resolved to baseline (pretreatment) grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse event.

The schedule of follow-up visits and assessments is provided in Appendix 1 and Appendix 2.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as failure to comply with the protocol requirements for assessments of safety and efficacy of the study medications, as well as failure to comply with study drug administration

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Drug Discontinuation

Patients must discontinue study drug if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if the patient continues to receive study drug
- Pregnancy
- Documented disease progression or relapse
- Unacceptable toxicity
- Use of another anti-cancer therapy
- Patient or investigator decision

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The GDC-0810 entire safety profile is not known at this time. Human experience is currently limited, and the identified and potential risks of GDC-0810 described below are based on nonclinical data (in vitro and in vivo), clinical data from the first 41 patients enrolled on Study GO29642 *Phase Ia* (single-agent, dose-escalation study), and published data on similar molecules. The safety of participating patients will be addressed through appropriate choice of inclusion/exclusion criteria, the implementation of appropriate dose-modification and treatment guidelines, and real-time safety monitoring and assessments on individual adverse-event reports.

Prior to halt of enrolment, an IMC monitored the safety of the two study arms. Safety profiles observed from the treated patients were consistent with the known safety profiles of GDC-0810 and fulvestrant, and no new safety findings had been identified.

No further patients will be enrolled in this study and the remaining patients on study will be re-consented. Following unblinding of the study team, halt of enrollment, given the IMC concluded that the safety profiles were consistent with the known profiles of the two drugs, and no further increase in the sample size, the IMC will no longer monitor individual patient safety; instead, the Sponsor will continue to monitor clinical safety data in real time.

5.1.1 Safety Monitoring

Safety will be evaluated through the monitoring of all serious and non-serious adverse events defined and graded according to NCI CTCAE, v4.0, as well as laboratory test findings. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistry and blood counts (see Appendix 1 for the schedule of study assessments). All serious adverse events and protocol-defined adverse events of special interest will be reported to the Sponsor in an expedited fashion (see Section 5.2).

The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.1.2 Internal Monitoring Committee

As of protocol version 2 and unblinding of the study team, the IMC will no longer be required to monitor the ongoing safety of the study; however, the study team will continue to monitor clinical safety data in real time (see Section 5.1).

5.1.3 Identified Safety Risks Associated With GDC-0810

5.1.3.1 Gastrointestinal Toxicities (Diarrhea, Nausea and Vomiting)

GI toxicities such as diarrhea, nausea and vomiting have been commonly observed in patients receiving single-agent GDC-0810. As of a data cutoff of *9 September 2016, safety data was available from 107 patients treated with GDC-0810 600 mg in the Phase IIa and non-palbociclib containing Phase 1b components of Study GO29642. T*reatment-related diarrhea, nausea, and vomiting were observed in *44%, 38%, and 13% of the 107* patients, respectively. Most of these GI events were Grade 1 or 2 in severity *and* occurred as early as in the first cycle of treatment. These GI events were typically manageable with dietary modifications (e.g., taking GDC-0810 with food), and supportive care as needed (e.g., loperamide for diarrhea). Dose interruption *was required in 11 of the 60 patients who experienced diarrhea, among the 107 patients.*

Patients with active inflammatory bowel disease, short bowel syndrome, or gastric resection are excluded from this study. Patients should be closely monitored for *signs and symptoms related to GI effects*. Patients experiencing nausea, vomiting, and diarrhea should be *treated as per Table 1*.

Any cases of Grade ≥2 diarrhea/vomiting or Grade ≥3 nausea, regardless of seriousness or causality, should be reported immediately to the Sponsor (see Section 5.2.3).

5.1.4 Potential Safety Risks Associated with GDC-0810

5.1.4.1 Changes in the Female Reproductive *Organs and Uterotrophic Effects*

GDC-0810 exhibited mixed antagonist/agonist activity in the rat uterus that was intermediate between tamoxifen and raloxifene. In adult ovariectomized rats, an increase in uterine weight and endometrial cell height was observed following treatment with GDC-0810 (refer to the GDC-0810 Investigator's Brochure, Version 4 for further details).

As of the data cutoff of 9 September 2016, safety data from 148 patients treated with GDC-0810 in the Phase Ia, IIa, and non-palbociclib containing Ib components of Study GO29642 were reviewed. Among 36 patients with a baseline transvaginal ultrasound scan of the uterus and at least one follow up scan, 29 (81%) patients showed an increase in the thickness of endometrium in their most recent postbaseline scan compared with their baseline thickness. The median change in thickness from screening to most recent measurement was 3 mm (range –1.7 to 44 mm), and the mean was 5 mm. Two of the 148 patients experienced Grade 1 adverse events of vaginal hemorrhage. One event followed an endometrial biopsy and was considered unrelated to GDC-0810. The second event was considered related to GDC-0810 and a cyst was noted on ultrasound, which may have been the cause of bleeding. Endometrial polyps were reported as adverse events in 3 patients.

Among the 148 patients, reproductive organ adverse events (occurring under the MedDRA SOC reproductive system and breast disorders), regardless of relatedness included vaginal discharge that was reported in 27 (18%) patients, ranging from Grade 1 to 2 in severity and was of Grade 1 severity in 25 of 27 patients.

Every precaution should be taken to ensure that no pregnant woman receives GDC-0810.

Given the potential effect of GDC-0810 on the uterus, patients with a history of endometrial cancer or atypical endometrial hyperplasia are excluded from participating in this study. Transvaginal ultrasound scans will be performed in patients to monitor endometrial thickness (at baseline, at the study drug discontinuation visit, and as clinically indicated). No action is required for asymptomatic endometrial thickening. Patients experiencing any abnormal vaginal bleeding post-study treatment are advised to seek consultation with their gynecologist for complete gynecological workup. Any cases of treatment-emergent Grade ≥2 vaginal or uterine hemorrhage regardless of seriousness or causality should be reported immediately to the Sponsor (see Section 5.2.3).

All patients will be made aware of the potential risk to their reproductive tract at the time of consent. *See Table 1 for management of vaginal or uterine hemorrhage.*

5.1.4.2 Venous Thromboembolic Events

An increased risk of VTE is known to be associated with some endocrine therapies such as tamoxifen.

As of a data cutoff of 9 September 2016, safety data from 148 patients treated with GDC-0810 in the Phase Ia, IIa, and non-palbociclib containing Ib components of Study GO29642 were reviewed. Among the 148 patients, 9 experienced at least one adverse event of thromboembolism (defined by MedDRA SMQ narrow of embolic and thrombotic events, venous). Preferred terms were deep vein thrombosis, pulmonary embolism and venous thrombosis. Events ranged from Grade 2 to 4 in severity, and all were treated with anticoagulation.

Patients should be advised to seek immediate medical attention if they become aware of any symptoms of pulmonary embolism or deep vein thrombosis, such as acute onset of chest pain, shortness of breath, or swelling in extremities. *Investigators should manage and treat patients suspected to have a VTE according to Table 1.*

Thromboembolic events (e.g., pulmonary embolism, deep vein thrombosis) of Grade ≥2, regardless of seriousness or causality, should be reported immediately to the Sponsor (see Section 5.2).

See Table 1 for guidelines on the management of VTEs.

5.1.4.3 Renal Dysfunction

Nonclinical toxicity studies have demonstrated minimal-to-mild microscopic findings in animal kidneys (kidney tubular degeneration, dilation, mineralization), which were completely reversible upon cessation of study drug. *As of 9 September 2016, the adverse event term of acute kidney injury was reported in 2 (1.3%) patients across all phases of Study GO29642 (combined n=148), neither case was considered related to GDC-0810.*

Renal function tests will be closely monitored, and GDC-0810 treatment should be held for Grade ≥2 creatinine elevation. GDC-0810 may be resumed if creatinine improves to normal or baseline value, whichever is higher.

5.1.4.4 Phototoxicity

An in vitro study demonstrated the potential of GDC-0810 for phototoxicity. As of 9 September 2016, no adverse events of photosensitivity reactions have been reported in the Phase Ia/IIa of Study GO29642.

Patients should be advised to take precautionary measures regarding sun exposure, with daily sunscreen use and wearing of protective clothing (i.e., sunglasses, hat, and long sleeves) when outdoors.

5.1.4.5 *Elevation of Hepatic Transaminases*

Endocrine therapy of metastatic breast cancer has been associated with changes in hepatic enzyme levels and rare instances of severe events including hepatic necrosis (fulvestrant [Faslodex®] Package Insert; tamoxifen [Nolvadex®] Package Insert). In cynomolgus monkeys, increased liver weight and hepatocyte hypertrophy have been observed after administration of GDC-0810.

Hepatic transaminase elevation has been observed in patients receiving GDC-0810. As of the data cutoff of 9 September 2016, safety data from 148 patients treated with GDC-0810 in the Phase Ia, IIa, and non-palbociclib containing Ib components of Study GO29642 were reviewed. Among the 148 patients, 7 patients experienced at least 1 Grade ≥ 3 adverse event under the higher level MedDRA term of liver function analyses. Among these 7 patients, 5 had evidence of metastases in their liver. Of the remaining 2, 1 patient who was enrolled in the Phase IIa (600 mg QD, with food) experienced a maximum Grade 3 transaminase elevation (both ALT and AST). ALP and bilirubin were not elevated above the normal range. The patient experienced three episodes of transaminase elevation. Each resolved after treatment interruption of GDC-0810. The third elevation occurred at the reduced dose of 400 mg OD of GDC-0810, leading to the withdrawal of treatment. The second patient experienced Grade 3 liver enzyme elevation during a respiratory tract infection on concomitant antibiotics.

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 liver enzymes are elevated with no obvious malignant cause found, a hepatologist specialist should be consulted.

Patients experiencing hepatic transaminase elevation of Grade ≥ 3, regardless of seriousness or causality, should be reported immediately to the Sponsor (see Section 5.2).

Patients experiencing hepatic enzyme elevation should be treated and managed per standard of care and Table 1.

5.1.4.6 General Guidance for GDC-0810 Dose Modifications

The GDC-0810 dose-reduction instructions provided here are intended to serve as recommended guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression, while monitoring patient safety. In addition to these guidelines, more conservative drug interruptions or dose reductions for the management of adverse events are permitted at the discretion of the investigator when deemed to be in the best interest of the patient.

GDC-0810 should be held in the presence of Grade ≥2 creatinine elevation

Any Grade ≥3 adverse events potentially attributed to the study drug. *Further detailed guidelines are provided in Section 5.1.3, 5.1.4.1–5.1.4.5, and Table 1.*

Patients who have had treatment interruptions due to adverse events may restart daily dosing as per the investigator's discretion when toxicity has resolved to Grade ≤1 or baseline. However, any patient whose treatment is interrupted for an adverse event that is related to study drug and who does not restart treatment within 28 days will be withdrawn from study treatment.

Dose reductions for toxicity will be allowed at the investigator's discretion, and in consultation with the Sponsor Medical Monitor. No more than two dose reductions will be allowed. 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 Medical Monitor. GDC-0810 dose reductions may occur in increments of 200 mg. Therefore, the possible GDC-0810 doses permitted are 600 mg, 400 mg, and 200 mg.

Table 1 Dose Management Guidelines for GDC-0810

Toxicity	*Dose Modification and Management Guidelines*
Gastrointestinal Toxicities	
General	• *Patients should be closely monitored for 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).*
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.* • *Hold 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).*

Toxicity	*Dose Modification and Management Guidelines*
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.* • *Upon resolution, consider starting loperamide 2 mg 1–2 times daily as secondary prophylaxis (i.e., use of loperamide to prevent further diarrhea).*
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.*
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.*

Toxicity	*Dose Modification and Management Guidelines*
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.*
Venous Thromboembolic Events (including Pulmonary Embolism):	
General	• *Patients should be advised to seek immediate medical attention if they become aware of any symptoms of PE or 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 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.*
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 specialist should be consulted.* • *Patients experiencing hepatic enzyme elevation should be treated and managed per standard of care.* *Per Section 5.3.5.6, investigators must report the occurrence of abnormal liver function tests meeting Hy's law criteria as an adverse event.*
Grade ≥ 3	• *Hold study drug until resolution to baseline or below ULN.*

AESI =adverse event of special interest (see Section 5.2.3); DVT =deep vein thrombosis; GI = gastrointestinal; IVC =inferior vena cava; PE =pulmonary embolism; VTE =venous thromboembolic event; ULN =upper limit of normal.

5.1.5 Safety Risks Associated with Fulvestrant

In a Phase III randomized, double-blind, clinical trial that compared a 500-mg dose of fulvestrant with a 250-mg dose in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease, the most frequently reported adverse events in the 500-mg group were injection-site pain (11.6% of patients),

nausea (9.7%), and bone pain (9.4%); in the 250-mg group, they were nausea (13.6%), back pain (10.7%), and injection-site pain (9.1%). In the pooled safety population from clinical trials comparing fulvestrant 500 mg to 250 mg, postbaseline increase of Grade $\geq$ 1 AST, ALT, or ALP were observed in $>$ 15% of patients, with Grade 3 – 4 increases in 1% – 2% of patients. Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

For more details regarding the safety profile of fulvestrant, please refer to the fulvestrant (e.g., FASLODEX®) Package Insert or SmPC.

5.1.5.1 General Guidance for Fulvestrant Dose Modifications

The fulvestrant dose level cannot be modified. In general, the investigator may consider continuing fulvestrant if the observed adverse event is not thought to be fulvestrant related.

If a scheduled dose coincides with a holiday or inclement weather or other conditions that preclude dosing, dosing should commence on the nearest following date. Subsequent dosing should continue on the original 28-day schedule.

5.2 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 5.4.

5.2.1 Adverse Events

According to the ICH guidelines for 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 in Section 5.3.5.9
- 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)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is 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 5.3.5.10)
- 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)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a 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 criteria; see Section 5.3.3); 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 5.4.2 for reporting instructions).

5.2.3 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 (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- 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 5.3.5.6)
- 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.
- Grade ≥ 2 diarrhea or vomiting
- Grade ≥ 3 nausea
- Grade ≥ 2 vaginal or uterine hemorrhage (Grade 2 is defined as moderate bleeding; medical intervention indicated)
- Grade ≥ 2 thromboembolic event (*including* pulmonary embolism)
- *Grade ≥3 elevation of ALT or AST*

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 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 5.4 to Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 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 5.4.2 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 5.6).

5.3.2 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?"

5.3.3 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 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 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 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 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 3):

- 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 3 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).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 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.

5.3.5.1 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.

5.3.5.2 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 GI 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.

5.3.5.3 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 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 5.4.2 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.

5.3.5.4 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., ALP 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 5.3.5.4 for details on recording persistent adverse events).

5.3.5.5 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 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 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 $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value 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 5.3.5.1) 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 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of malignant 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 malignant breast cancer, "malignant disease 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 5.6.

5.3.5.8 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").

5.3.5.9 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 modified RECIST v1.1. 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.

5.3.5.10 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 5.2.2), 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 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
- Hospitalization due solely to progression of the underlying cancer
- Hospitalization for outpatient care outside of normal clinical operating hours that is required per protocol or per local standard of care

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

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*

5.3.5.11 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 5.4.2).

No safety data related to overdosing of GDC-0810 are available.

5.3.5.12 Adverse Events that Change Grade over Time

When a patient experiences an adverse event that later increases in grade, the increased grade should be recorded on the Adverse Event eCRF. In general, subsequent adverse-event grade decreases (with the exception of resolution) should not be recorded on the Adverse Event eCRF, as maximum grade is of primary interest for safety reporting. However, any additional upgrades and downgrades of diarrhea outside of the initial and maximum grade should be recorded on the Adverse Event Grade Changes eCRF to more fully assess the impact of time and/or supportive care on diarrhea symptoms.

5.3.5.13 Patient-Reported Outcome Data

Adverse-event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Because of these differences, PRO data will not be reported as adverse events, and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events. The PRO data will be presented in separate tables, figures, and data listings from the adverse-event data, and will be included in the appropriate section of the final study report.

5.4 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 5.4.2 for further details)
- Non-serious adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 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).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Primary (PPD) Medical Monitor contact information:

Medical Monitors:	[redacted], M.D. (primary)
	[redacted], M.D. (secondary, Europe)
	[redacted], M.D. (secondary, Asia/Pacific)
Telephone Nos.:	[redacted] (North America)
	[redacted] (Europe and Asia/Pacific)
Facsimile Nos.:	[redacted] (North America)
	[redacted] (Europe and Asia/Pacific)

Alternate (Genentech) Medical Monitor contact information for all sites:

Medical Monitor:	[redacted], *M.D., Ph.D.*
Telephone No.:	[redacted] ([redacted], USA)
Alternate Telephone No.:	[redacted] ([redacted], USA)

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

5.4.2.1 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 *to Genentech via PPD at the following contact information:*

Email:	*rtpsafety@ppdi.com*
Telephone Nos.:	*800.201.8725 (North America)*
	44.1223.374.240 (Europe and Asia/Pacific)
Facsimile Nos.:	*888.488.9697 (North America)*
	44.1223.374.102 (Europe and Asia/Pacific)

5.4.2.2 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. Investigators 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), by faxing the form using the fax number or email address provided above in Section 5.4.2.1. 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 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Patients 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 *or 1 year after the last dose of fulvestrant*. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. 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 the event that the EDC system is unavailable, the Clinical Trial Pregnancy 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 pregnancy), by faxing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 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 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 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. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 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.

5.6 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.

5.7 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 using the following reference documents:

- GDC-0810 Investigator's Brochure
- SmPC for fulvestrant

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Primary and secondary efficacy analyses will include all randomized patients, with patients allocated to the randomized treatment arm. In addition to the all-randomized patient population (the ITT population), analysis of PFS, ORR, and CBR will be repeated in the patient subsets defined by their *ESR1* mutation status.

Safety analyses will include all patients who received at least one dose of the study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

There will be no adjustments made for multiple comparisons when analyzing the primary and secondary endpoints.

6.1 DETERMINATION OF SAMPLE SIZE

The trial is designed to evaluate the clinical activity and safety of GDC-0810 compared with fulvestrant in patients with ER-positive locally advanced or MBC. It is for hypothesis generation, and is not powered to detect minimum clinically meaningful difference between treatment arms.

A total of approximately 152 patients will be enrolled in this study. It is assumed that the median duration of PFS in the fulvestrant control arm is 5.5 months and 8.5 months in the GDC-0810 arm. The final analysis of all randomized patients will be triggered by the occurrence of approximately 95 PFS events, which is expected to occur 26 months after the first patient is randomized. Table 4 shows expected probabilities of observing a hazard ratio of less than 0.5, 0.6 and 0.7 in the final analysis in all randomized patients under varying assumptions for the true underlying hazard ratio. Note that formal hypothesis testing is limited. Rather than testing treatment differences at a statistically significant type I error level of 5%, 90% confidence intervals (CI) for the hazard ratio will be calculated.

At a target hazard ratio of 0.6, the corresponding 90% CI based on 95 PFS events is (0.43, 0.84) which is considered to provide meaningful precision.

Table 4 Expected Probability of Observing a Hazard Ratio of <0.5, <0.6, or <0.7 in the Final Analysis (All Patients)

	95 PFS Events in ITT Population		
True HR	Observed HR $<$ 0.50	Observed HR $<$ 0.60	Observed HR $<$ 0.70
0.4	0.86	0.98	0.99
0.5	0.50	0.81	0.95
0.6	0.19	0.50	0.77
0.7	0.05	0.23	0.50
0.8	0.01	0.08	0.26

HR = hazard ratio; ITT = intent to treat; PFS = progression-free survival.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration and discontinuation from the study will be summarized by treatment arm. The incidence of study treatment discontinuation for reasons other than disease progression will be assessed.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables, stratification factors, and other baseline characteristics will be summarized by treatment groups.

Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum and maximum. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments using RECIST v1.1 or death on study from any cause. The primary efficacy analyses will be performed on all randomized patients as well as on patients with *ESR1* LBD mutations detected in circulating cell-free DNA, with patients allocated to the treatment arm assigned at randomization.

For patients without disease progression or death as of the clinical data cutoff date, their PFS will be censored at the time of last tumor assessment (or censored at the date of randomization, if no tumor assessment was performed after the baseline visit). For patients who start other anti-cancer treatment prior to the documented PFS event, the primary PFS analysis will include PFS events after other anti-cancer treatment. PFS

sensitivity analysis will be performed, censoring PFS on the last tumor assessment prior to starting other anti-cancer therapy.

The two-sided log-rank test stratified by the stratification factors will be used as the primary analysis. The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. Cox proportional hazards models stratified by the stratification factors will be used to estimate a hazard ratio and its 90% CI. The results from the unstratified analysis will also be provided.

Exploratory analysis for PFS may be performed on patient subgroups by demographic disease characteristics.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Objective Response Rate

The analysis of ORR will only include patients who have measurable disease at baseline (and will thus exclude patients with bone-only disease). An estimate of the response rate and its 90% CI will be calculated using the Blyth-Still-Casella method for each treatment arm. Response rate in the treatment arms will be compared using the stratified Mantel-Haenszel test. CIs for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution.

6.4.2.2 Duration of Objective Response

DOR is defined as the time from first observation of an objective response until first observation of disease progression as assessed by the investigator according to RECIST v1.1 or death from any cause. The analysis of DOR will include only patients who achieved an objective response.

DOR will be estimated using the Kaplan-Meier methodology, with patients grouped according to the treatment arm assigned at randomization. Comparisons between treatment arms using stratified and unstratified log rank test will be made for descriptive purposes. Because the determination of DOR is based on a nonrandomized subset of all patients, formal hypothesis testing will not be performed.

6.4.2.3 Clinical Benefit Rate

CBR is defined as the percentage of patients who experience a CR, PR, or SD lasting for at least 24 weeks since randomization. An estimate of CBR and its 90% CI will be calculated using the Blyth-Still-Casella method for each treatment arm. The CBRs in the treatment groups will be compared using the stratified Mantel-Haenszel test. CIs for the difference in CBR between the two arms will be determined using the normal approximation to the binomial distribution.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received at least one dose of study drug, with patients grouped according to the treatment actually received. Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, and GDC-0810 exposure.

Drug exposure will be summarized, which includes duration of treatment, number and intensity of dose.

Verbatim descriptions of adverse events will be mapped to thesaurus terms. Adverse-event data will be listed by study site, treatment arm, patient number, and study day. All adverse events occurring during or after the first dose of study treatment will be summarized by thesaurus term, appropriate thesaurus levels, treatment arm, and NCI CTCAE v4.0 grade. In addition, serious adverse events, severe adverse events (Grade $\geq$ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be listed separately and summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Deaths reported during the study will be summarized by treatment arm, including reasons leading to death.

Relevant laboratory and vital sign (heart rate, blood pressure, and temperature) data will be displayed by time, with NCI CTCAE Grades 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized by NCI CTCAE v4.0 grade.

6.6 PHARMACOKINETIC ANALYSES

As outlined in Appendix 3, plasma PK samples will be obtained for GDC-0810 *and plasma concentrations will be summarized by visit*. Population PK analysis *may* be performed to characterize the PK in this study. Additionally, population PK/PD analysis may be performed to assess potential correlations of exposure with dose, demographics, PD, safety, and efficacy outcomes. The results of these population analyses may be reported separately from the clinical study report.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

The percentage of participants randomized to each treatment group who complete each measure at baseline and each subsequent assessment point (i.e., PRO completion rates) will be calculated and compared. Summary statistics (mean, standard deviation, median, and range) of absolute scores and the change from baseline will be reported for all items and subscales of the EORTC QLQ-C30 and QLQ-BR23 according to the EORTC scoring manual (Fayers et al. 2001). Descriptive statistics (means) will be used to display the results of the modified version of the TSQM subscales (side effects, convenience, and global satisfaction), and responses obtained while receiving

GDC-0810 treatment will be compared to responses obtained to patients receiving fulvestrant (Atkinson et al. 2004).

In the event of incomplete data, if the scale has more than 50% of the constituent items completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers of the measure. For subscales with less than 50% of the items completed, the subscale will be considered missing.

6.8 ADDITIONAL EXPLORATORY ANALYSES

The analysis of OS will be conducted in all randomized patients. Data for patients who are alive at the time of analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of randomization plus 1 day. The OS curve for each treatment arm will be estimated by the Kaplan-Meier methodology, and the hazard ratio and its 90% CI will be estimated by the Cox proportional-hazards model.

Exploratory biomarker analyses may be performed in an effort to understand the association of these markers with study-treatment response.

Whole genome sequencing data will be analyzed in the context of this study and explored in aggregate with other studies to better understand disease pathobiology and guide the development of new therapeutic approaches.

Blood samples may be used for the evaluation of genetic polymorphisms of drug metabolic enzymes, such as CYP3A4/5 and UGT1A1; transporters, such as OATP1B1 and BCRP; and genetic variants, which could contribute to potential drug-safety assessments.

6.9 INTERIM ANALYSIS

The IMC will convene for an interim safety analysis to review unblended summaries of the safety and PK data after the first 20 patients are randomized and have completed two 28-day cycles of therapy.

In addition, after occurrence of approximately 62 PFS events in all patients, the IMC may convene to perform an interim analysis for safety and efficacy. This interim efficacy analysis likely will not be informative for the *ESR1* mutant subset because of the insufficient number of patients with *ESR1* mutant tumors who are projected to have experienced disease progression by that time. The activity of GDC-0810 versus fulvestrant in the *ESR1* mutant subset will be assessed at interim only if a reasonable number of PFS events is available in the subset (for example, 30 PFS events).

Table 5 shows the probability of observing a hazard ratio of less than 0.5, less than 0.6, or 0.7 at interim analysis under varying assumptions of the true underlying hazard ratio for all patients.

Table 5 Interim Analysis (All Patients)

	62 PFS Events in ITT		
True HR	Observed HR < 0.50	Observed HR < 0.60	Observed HR < 0.70
0.4	0.81	0.94	0.99
0.5	0.50	0.76	0.91
0.6	0.24	0.5	0.73
0.7	0.09	0.27	0.50
0.8	0.03	0.13	0.30

HR = hazard ratio; ITT = intent to treat; PFS = progression-free survival.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor and a CRO will share responsibility for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an ePRO device to capture PRO data. The data will be transmitted electronically to a centralized database at the ePRO vendor. This electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data can be reviewed by site staff via secure access to a web portal. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP 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 or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample ICFs, such as a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final

IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, the Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. 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 health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 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.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 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.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech and will be managed by a CRO. The CRO will provide clinical operations management, data management, and medical monitoring support to the Sponsor. Approximately 45 sites in North America, Europe, and Asia Pacific will participate to enroll approximately 152 patients.

After written informed consent has been obtained and eligibility has been established, the study site will obtain the patient's unique identification number and treatment assignment from the IWRS. The IWRS will manage GDC-0810 and fulvestrant inventory at all sites. IWRS will be required to randomize patients, to monitor enrollment and patient status, and to manage study treatment requests and shipments.

PRO data will be elicited from all patients in the study to more fully characterize the patient profile. The PRO data will be collected electronically in the local languages of each participating country (see Section 4.5.8).

Patient data will be recorded via an EDC system from Medidata Solutions through use of eCRFs (see Section 7.2).

Central laboratories will provide kits for PK, pharmacogenomic, tissue, whole blood, and plasma sample analyses to be conducted at central laboratories or Genentech or third-party laboratories.

An independent radiologic review facility will be used for the purpose of collecting and assessing the quality of patient scans in a standardized fashion throughout the trial. The review facility will retain copies of scans for potential centralized assessments of response or progression in the future.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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.

9.6 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).

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2004;2:12.

Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor positive advanced breast cancer. N Engl J Med 2012 9;366:520 – 9.

Cardoso F, Harbeck N, Fallowfield L, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;(23 Supplement 7):vii11–19.

Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 2008;26:1664 – 70.

Diehl F, Schmidt K, Durkee KH, et al. Analysis of mutations in DNA isolated from plasma and stool of colorectal cancer patients. Gastroenterology 2008;135:489 – 98.

Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-postiive advanced breast cancer. J Clin Oncol 2010; 28:4594 – 600.

Dupont Jensen J, Laenkholm AV, Knoop A, et al. PIK3CA mutations may be discordant between primary and corresponding metastatic disease in breast cancer. Clin Cancer Res 2011;17:667 – 77.

Faslodex® (fulvestrant) injection Package Insert, AstraZeneca.

Fayers PM, Aaronson NK, Bjordal K, et al. On behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

Gonzalez-Angulo AM, Ferrer-Lozano J, Stemke-Hale KA, et al. PI3K pathway mutations and PTEN levels in primary and metastatic breast cancer. Mol Cancer Therapeutics 2011;10:1093 – 101.

Howell A, Osborne CK, Morris C, et al. ICI 182,780 (Faslodex): development of a novel, “pure” antiestrogen. Cancer 2000;89:817 – 25.

Howell A, Robertson FJ, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 2002;20:3396 – 403.

Howell A, Roberston JF, Abram P, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. J Clin Oncol 2004;22:1605 – 13.

Jemal A, Bray F, Center MM, et al. Global cancer statistics. Ca Cancer J Clin 2011; 61:69 – 90.

Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol 2013;14:989 – 98.

Koenders PG, Beex, LV, Kloppenborg PW, et al. Human breast cancer: survival from first metastasis. Breast Cancer Study Group 1992;21:173 – 80.

Li S, Shen D, Shao J, et al. Endocrine-therapy-resistant ESR1 variants revealed by genomic characterization of breast-cancer-derived xenografts. Cell Rep 2013;4:1116 – 30.

Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. N Engl J Med 2008;359:366 – 77.

Miller TW, Hennessy BT, González-Angulo AM, et al. Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. J Clin Invest 2010;120:2406 – 13.

Nolvadex® (tamoxifen) Package Insert, AstraZeneca.

O'Dwyer PJ and Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. J Clin Oncol 2006;24:4534 – 8.

Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 2002;20:3386 – 95.

Osoba D, Aaronson N, Zee B, et al. Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. Qual Life Res 1997;6:103–8.

Robertson JF, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. J Clin Oncol 2009;27:4530–5.

Robinson DR, Wu YM, Vats P, et al. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet 2013;45:1446–5.

Sanchez CG, Ma CX, Crowder RJ, et al. Preclinical modeling of combined phosphatidylinositol-3-kinase inhibition with endocrine therapy for estrogen receptor-positive breast cancer. Breast Cancer Res 2011;13(2):R21.

Segal CV and Dowsett M. Estrogen receptor mutations in breast cancer – new focus on an old target. Clin Can Res 2014;20:1724–6.

Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996; 14:2756–68.

Toy Q, Shen Y, Won H, et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet 2013;45:1439–45.

Van Tine BA, Crowder RJ, Ellis MJ. ER and PI3K independently modulate endocrine resistance in ER-positive breast cancer. Cancer Discov 2011;1:287–8.

Appendix 1
Schedule of Assessments for Patients on Arm A (GDC-0810)

	Screening [a]	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycles 5+	Study Drug Discontinuation [b]
Day (Window)	−28 to −1	1	15 (+1) [c]	1 (+1) [c]	1 (±1) [c]	1 (±3) [c]	1 (±3) [c]	Within 30 days after last dose
Informed consent [d]	x							
Medical history and demographic data [e]	x							
Concomitant medications [f]	x	x	x	x	x	x	x [g]	x
Adverse events [h]	x	x	x	x	x	x	x [g]	x
Vital signs [i]	x	x	x	x	x	x	x	x
Complete physical examination, height, weight [j]	x							
Limited physical examination [k]		x	x	x	x	x	x	x
ECOG performance status	x	x	x	x	x	x	x	x
Single 12-lead ECG	x	As clinically indicated						x
Endometrial thickness assessment [l]	x	As clinically indicated						x
Tumor assessment [m]	x	x [g]						x
Bone scan [n]	x	x [g]						
Drug accountability		x	x	x	x	x	x	x
CBC with differential [o]	x	x	x	x	x	x	x [g]	x
Coagulation (INR, aPTT) [p]	x	As clinically indicated (see footnote)						
Blood chemistry [q]	x [q]	x	x	x	x	x	x [g]	x
FSH and estradiol	x [r]							
Urinalysis [s]	x	As clinically indicated						

Appendix 1
Schedule of Assessments for Patients on Arm A (GDC-0810) (cont.)

	Screening [a]	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycles 5+	Study Drug Discontinuation [b]
Day (Window)	−28 to −1	1	15 (+1) [c]	1 (+1) [c]	1 (±1) [c]	1 (±3) [c]	1 (±3) [c]	Within 30 days after last dose
Archival (or fresh) FFPE tumor tissue [t]	x							
Plasma sample for ctDNA and plasma biomarkers [u]		x			x		x	x
Plasma sample for potential CDx [v]		x			x			
Plasma sample for PK analysis [w]		x			x			
Blood sample for pharmacogenetics [x]		x						
Optional blood sample for WGS [y]		x						
Optional tumor biopsy at progression [z]								x
GDC-0810 administration [aa]		x	x	x	x	x	x	

Appendix 1
Schedule of Assessments for Patients on Arm A (GDC-0810) (cont.)

aPTT = activated partial thromboplastin time; CBC = complete blood count; CDx = companion diagnostic; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organization for Research and Cancer; FFPE = formalin-fixed, paraffin-embedded; FSH = follicle stimulating hormone; INR = international normalized ratio; PK = pharmacokinetic; PRO = patient-reported outcome; TSQM = Treatment Satisfaction Questionnaire for Medication; q12 = every 12 (weeks); QLQ-BR23 = Quality Of Life Questionnaire Breast Cancer Module; QLQ-C30 = Quality Of Life Questionnaire; WGS = whole genome sequencing.

Notes: All assessments should be performed within the indicated window unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Patients should receive their first dose of study treatment on the day of randomization if possible, but no later than 5 business days after randomization.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study drug for any reason other than death will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study drug. Patients must be followed for safety assessment for at least 28 days after completion of study drug. The visit at which response assessment shows disease progression may be used as the study drug discontinuation visit, provided that all tests required at the study drug discontinuation visit are performed.

[c] The visit window for Cycle 1 Day 15 and Cycle 2 Day 1 is +1 day, because fulvestrant administration should not occur prior to Cycle 1 Day 15 or Cycle 2 Day 1. The visit window for Cycle 3 Day 1 is +1 day, and the visit window for Day 1 of Cycles 4 and up is ±3 days. Visits are based on a 28-day cycle. If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend that precludes the procedure within the allotted window, the procedure must be performed on the nearest following date. The date of Cycle 1 Day 1 should be used to calculate all subsequent target visit dates.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Medical history includes clinically significant diseases within the previous 5 years before Cycle 1 Day 1, smoking history and breast cancer history (including tumor characteristics such as hormone receptor status, prior cancer therapies, surgeries and procedures). Demographic data include age, sex, and self-reported race/ethnicity where allowed by local regulatory authorities.

[f] Concomitant medications include prescription medication, over-the-counter preparations, and herbal or homeopathic remedies and supplements used within 7 days prior to the screening visit through the study drug discontinuation visit. After the study drug discontinuation visit, only medications administered for ongoing or new treatment-related adverse events or as anti-cancer therapy will be collected.

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

Appendix 1
Schedule of Assessments for Patients on Arm A (GDC-0810) (cont.)

[h] 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. After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug. 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. Please note, additional information will be collected if diarrhea is reported as an adverse event.

[i] Vital signs include measurements of heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and oral or tympanic temperature. Record abnormalities on the Adverse Event eCRF.

[j] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[k] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Transvaginal ultrasounds should be performed to monitor endometrial thickness during the study at screening, at the study drug discontinuation visit, and additionally when clinically indicated (e.g., to evaluate vaginal bleeding). *Transvaginal ultrasounds are not required for patients who have had a hysterectomy.*

[m] Perform tumor assessments at screening *per institutional guidelines* and additionally when clinically indicated for all patients. Screening assessments must include CT scans of the chest, abdomen and pelvis; CT scans of the neck and brain imaging should be included if clinically indicated. A documented standard-of-care tumor assessment performed within 28 days before Cycle 1 Day 1 may be used for the screening assessment, provided it meets the above requirements. The same imaging method used at screening must be used throughout the study. Response assessments will be performed by the investigator, on the basis of physical examinations and imaging scans. Bone disease identified on bone imaging should be evaluated radiographically by CT scan, magnetic resonance imaging (MRI), or X-ray. The same modality used at screening should be used throughout the study.

[n] An isotope bone scan (e.g., technetium) will be performed at screening and should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions or for confirmation of complete response for all patients. For patients with bone-only disease not visible on the CT or MRI scans being performed as part of the tumor assessments, bone scans should be repeated when clinically indicated until disease progression.

[o] Includes white blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), red blood cell (RBC) count, hemoglobin, hematocrit, and platelet count. Reporting the differential as absolute counts is preferred, but percent is accepted. Pre-dose laboratory samples may be drawn within 2 days prior to the cycle visit (except Cycle 1 Day 1, which must be drawn at that visit).

[p] aPTT and INR should be collected at screening and as clinically indicated thereafter. For patients taking warfarin or its equivalent, aPTT and INR should be measured twice in the first week of administration and then as clinically indicated.

Appendix 1
Schedule of Assessments for Patients on Arm A (GDC-0810) (cont.)

[q] Blood chemistry includes the following: glucose, blood urea nitrogen or urea, creatinine, sodium, potassium, chloride, magnesium, bicarbonate, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, AST, and ALT. Samples for blood chemistry should be drawn predose, and may be drawn within 2 days prior to the cycle visit (except Cycle 1 Day 1, which must be drawn at that visit). Screening blood chemistry should be drawn after fasting (≥8 hours) at treatment and at the Study Drug Discontinuation Visit, but may be drawn nonfasting at all other time points.

[r] FSH and estradiol to be collected only when required to assess study eligibility (see Section 4.1.1).

[s] Urinalysis includes dipstick macro (specific gravity, pH, glucose, protein, ketones and blood). A reflex microscopic urinalysis (RBCs, WBCs, casts, etc.,) should be performed if the macroscopic analysis is abnormal.

[t] Archival tumor tissue blocks or a minimum of 10 (15 – 20 preferred) freshly cut unstained slides from the most recent tumor tissue will be collected at screening for molecular characterization of the tumor tissue including, but not limited to, *ESR1* mutations.

[u] A plasma sample will be collected for ctDNA and plasma biomarkers, including but not limited to *ESR1* mutations, *PIK3CA* mutations, and *AKT1* mutations on Day 1 of Cycle 1, Cycle 3, Cycle 5, Cycle 7, Cycle 9, and every 3 cycles thereafter, timed to coincide roughly with response assessments. On Cycle 1 Day 1, sample should be collected prior to study drug treatment.

[v] A plasma sample will be collected and banked for potential future blood-based companion diagnostic development. On Cycle 1 Day 1, sample should be collected prior to study drug treatment.

[w] See Appendix 3 for detailed schedule.

[x] A pharmacogenomics sample will be collected where approved by local regulatory authorities. On Cycle 1 Day 1, samples should be collected prior to study drug treatment.

[y] Collection of a blood sample for whole genome sequencing (see Section 4.5.10) is not required for study participation but is strongly encouraged and will be collected from patients who sign the Optional Research portion of the Informed Consent form. A blood sample will be collected as a source of normal DNA to determine whether sequence variants detected in tumor tissue are somatic mutations or single nucleotide polymorphisms. A portion of this sample will be used for WGS (see Section 4.5.10). Sample should be collected prior to study drug treatment. Not applicable for a site that has not been granted regulatory approval for WGS sampling.

[z] Tumor biopsy collection at the time of disease progression is not required for study participation but is strongly encouraged and will be collected from patients who sign the Optional Research portion of the Informed Consent Form.

[aa] GDC-0810 will be taken orally once daily beginning on Cycle 1 Day 1. GDC-0810 will be administered in the clinic on each day that a clinic visit is scheduled, after the predose assessments and procedures, and at home on all non-clinic visit days. A sufficient number of study drug tablets will be provided to last until the next visit. Patients will also receive a medication diary. Instruct the patient to record the time and date she takes each treatment dose in the diary and to return all unused tablets at each study visit, to assess compliance. Collect and review the medication diary and unused tablets and assess compliance at each visit after each visit. At the study drug discontinuation visit, do not dispense any additional study drug tablets or provide a new medication diary.

Appendix 2
Schedule of Assessments for Patients on Arm B (Fulvestrant)

	Screening [a]	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycles 5+	Study Drug Discontinuation [b]
Day (Window)	−28 to −1	1	15 (+1) [c]	1 (+1) [c]	1 (±1) [c]	1 (±3) [c]	1 (±3) [c]	Within 30 days after last dose
Informed consent [d]	x							
Medical history and demographic data [e]	x							
Concomitant medications [f]	x	x	x	x	x	x	x	x
Adverse events [g]	x	x	x	x	x	x	x	x
Vital signs [h]	x	x	x	x	x	x	x	x
Complete physical examination, height, weight [j]	x							
Limited physical examination [k]		x	x	x	x	x	x	x
ECOG performance status	x	x	x	x	x	x	x	x
Single 12-lead ECG	x	As clinically indicated						
Endometrial thickness assessment [l]	x	As clinically indicated						x
Tumor assessment [m]	x	*x* [i, n]						x
Bone scan [n]	x	Per clinical indication [n]						
CBC with differential [o]	x	x	x	x	x	x	x [i]	x
Coagulation (INR, aPTT) [p]	x	As clinically indicated (see footnote)						
Blood chemistry [q]	x [q]	x	x	x	x	x	x [i]	x [q]
FSH and estradiol [r]	x [r]							
Urinalysis [s]	x	As clinically indicated						
Archival (or fresh) FFPE tumor tissue [t]	x							

Appendix 2
Schedule of Assessments for Patients on Arm B (Fulvestrant) (cont.)

	Screening [a]	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycles 5+	Study Drug Discontinuation [b]
Day (Window)	−28 to −1	1	15 (+1) [c]	1 (+1) [c]	1 (±1) [c]	1 (±3) [c]	1 (±3) [c]	Within 30 days after last dose
Plasma sample for ctDNA and plasma biomarkers [u]		x			x		x	x
Plasma sample for potential CDx [v]		x			x			
Optional blood sample for WGS [w]		x						
Optional tumor biopsy at progression [x]								x
Fulvestrant administration [y]		x	x	x	x	x	x	

Appendix 2
Schedule of Assessments for Patients on Arm B (Fulvestrant) (cont.)

aPTT = activated partial thromboplastin time; CBC = complete blood count; CDx = companion diagnostic; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organization for Research and Cancer; FFPE = formalin-fixed, paraffin-embedded; FSH = follicle stimulating hormone; INR = international normalized ratio; PK = pharmacokinetic; PRO = patient-reported outcome; q12 = every 12 (weeks); QLQ-BR23 = Quality Of Life Questionnaire Breast Cancer Module; QLQ-C30 = Quality of Life Questionnaire; TSQM = Treatment Satisfaction Questionnaire for Medication; WGS = whole genome sequencing.

Notes: All assessments should be performed within the indicated window unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Patients should receive their first dose of study treatment on the day of randomization if possible, but no later than 5 business days after randomization.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study drug for any reason other than death will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study drug. Patients must be followed for safety assessment for at least 28 days after completion of study drug. The visit at which response assessment shows disease progression may be used as the study drug discontinuation visit provided that all tests required at the study drug discontinuation visit are performed.

[c] The visit window for Cycle 1 Day 15 and Cycle 2 Day 1 is +1 day since fulvestrant administration should not occur prior to Cycle 1 Day 15 or Cycle 2 Day 1. The visit window for Cycle 3 Day 1 is ±1 day and the visit window for Day 1 of Cycles 4 and up is ±3 days. Visits are based on a 28-day cycle. If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend that precludes the procedure within the allotted window, the procedure must be performed on the nearest following date. The date of Cycle 1 Day 1 should be used to calculate all subsequent target visit dates.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Medical history includes clinically significant diseases within the previous 5 years before Cycle 1 Day 1, smoking history and breast cancer history (including tumor characteristics such as hormone receptor status, prior cancer therapies, surgeries, and procedures). Demographic data include age, sex, and self-reported race/ethnicity where allowed by local regulatory authorities.

[f] Concomitant medications include prescription medication, over-the-counter preparations, and herbal or homeopathic remedies and supplements used within 7 days prior to the screening visit through the study drug discontinuation visit. After the study drug discontinuation visit, only medications administered for ongoing or new treatment-related adverse events or as anti-cancer therapy will be collected.

Appendix 2
Schedule of Assessments for Patients on Arm B (Fulvestrant) (cont.)

[g] 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. After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug. 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. Please note, additional information will be collected if diarrhea is reported as an adverse event.

[h] Vital signs include measurements of heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and oral or tympanic temperature. Record abnormalities on the Adverse Event eCRF.

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

[j] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[k] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Transvaginal ultrasounds should be performed to monitor endometrial thickness during the study at screening, at the study drug discontinuation visit, and additionally when clinically indicated (e.g., to evaluate vaginal bleeding). *Transvaginal ultrasounds are not required for patients who have had a hysterectomy.*

[m] Perform tumor assessments at screening *per institutional guidelines* and additionally when clinically indicated for all patients. Screening assessments must include CT scans of the chest, abdomen and pelvis; CT scans of the neck and brain imaging should be included if clinically indicated. A documented standard-of-care tumor assessment performed within 28 days before Cycle 1 Day 1 may be used for the screening assessment, provided it meets the above requirements. The same imaging method used at screening must be used throughout the study. Response assessments will be performed by the investigator, on the basis of physical examinations and imaging scans. Bone disease identified on bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray. The same modality used at screening should be used throughout the study.

[n] An isotope bone scan (e.g., technetium) will be performed at screening and should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions or for confirmation of complete response for all patients. For patients with bone-only disease not visible on the CT or MRI scans being performed as part of the tumor assessments, bone scans should be when clinically indicated until disease progression.

Appendix 2
Schedule of Assessments for Patients on Arm B (Fulvestrant) (cont.)

[o] Includes white blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), red blood cell (RBC) count, hemoglobin, hematocrit, and platelet count. Reporting the differential as absolute counts is preferred, but percent is accepted. Pre-dose laboratory samples may be drawn within 2 days prior to the cycle visit (except Cycle 1 Day 1, which must be drawn at that visit).

[p] aPTT and INR should be collected at screening and as clinically indicated thereafter. For patients taking warfarin or its equivalent, aPTT and INR should be measured twice in the first week of administration and then as clinically indicated.

[q] Blood chemistry includes the following: glucose, blood urea nitrogen or urea, creatinine, sodium, potassium, chloride, magnesium, bicarbonate, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, AST and ALT. Samples for blood chemistry should be drawn predose, and may be drawn within 2 days prior to the cycle visit (except Cycle 1 Day 1, which must be drawn at that visit). Screening blood chemistry should be drawn after fasting (≥8 hours) at treatment and at the study drug discontinuation visit, but may be drawn nonfasting at all other timepoints.

[r] FSH and estradiol to be collected only when required to assess study eligibility (see Section 4.1.1).

[s] Urinalysis includes dipstick macro (specific gravity, pH, glucose, protein, ketones and blood). A reflex microscopic urinalysis (RBCs, WBCs, casts, etc.,) should be performed if the macroscopic analysis is abnormal.

[t] Archival tumor tissue blocks or a minimum of 10 (15–20 preferred) freshly cut unstained slides from the most recent tumor tissue will be collected at screening for molecular characterization of the tumor tissue, including but not limited to *ESR1* mutations.

[u] A plasma sample will be collected for ctDNA and plasma biomarkers, including but not limited to *ESR1* mutations, *PIK3CA* mutations, and *AKT1* mutations on Day 1 of Cycle 1, Cycle 3, Cycle 5, Cycle 7, Cycle 9, and every 3 cycles thereafter, timed to coincide roughly with response assessments. On Cycle 1 Day 1, the sample should be collected prior to study drug treatment.

[v] A plasma sample will be collected and banked for potential future blood-based companion diagnostic development. On Cycle 1, Day 1, sample should be collected prior to study drug treatment.

[w] Collection of a blood sample for whole genome sequencing (see Section 4.5.10) is not required for study participation but is strongly encouraged and will be collected from patients who sign the Optional Research portion of the Informed Consent Form. A blood sample will be collected as a source of normal DNA to determine whether sequence variants detected in tumor tissue are somatic mutations or single nucleotide polymorphisms. A portion of this sample will be used for WGS (see Section 4.5.10). Not applicable for a site that has not been granted regulatory approval for WGS sampling.

[x] Tumor biopsy collection at the time of disease progression is not required for study participation but is strongly encouraged and will be collected from patients who sign the Optional Research portion of the Informed Consent Form.

[y] Fulvestrant will be administered in the clinic as two intramuscular injections of 250 mg each (total dose 500 mg) on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle.

Appendix 3
Schedule of Pharmacokinetic Assessments (for Arm A only)

Study Visit	Timepoint	Assessment
Cycle 1, Day 1	Predose	GDC-0810 PK
	3 hours postdose	GDC-0810 PK
Cycle 3, Day 1 (±1 day)	Predose	GDC-0810 PK
	3 hours postdose	GDC-0810 PK

Notes: Predose samples should be collected within 30 minutes before administration of GDC-0810. All other sample draw times are ±5 minutes. The plasma sample will be split into two equal aliquots: a primary sample and a back-up sample.

Detailed instructions for PK plasma sample preparation and shipping will be provided to the study sites in a separate Laboratory Manual.

Record exact date and time of all study drug doses and PK sample collections.

Appendix 7
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1,[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions and/or lymph nodes will be categorized as measurable or non-measurable as described below.

MEASURABLE TUMOR LESIONS

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and at follow-up, only the short axis will be measured and followed. See also notes below on “Baseline Documentation of Target and Non-Target Lesions” for information on lymph node measurement.

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

Appendix 7
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

NON-MEASURABLE TUMOR LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Appendix 7
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

Target Lesions: Specifications by Methods of Measurements

- Measurement of Lesions

  All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

- Method of Assessment

  The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality

and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally

reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$ 10 mm.

- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

Appendix 7
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (BML is equivalent to a “less than” sign.) (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

Appendix 7
Response Evaluation Criteria in Solid Tumors, V 1.1
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Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

All lymph nodes must be non-pathological in size ($<$10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits

PD: Unequivocal progression of existing non-target lesions

The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread, or may be described in

protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly, possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- A negative FDG-PET scan at baseline with a positive[3] FDG-PET scan during the study is a sign of PD based on a new lesion.
- In the case of no FDG-PET scan at baseline and a positive FDG-PET scan during the study:

[3] A "positive" FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation-corrected image.

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Modified Excerpt from Original Publication (cont.)

If the positive FDG-PET scan during the study corresponds to a new site of disease confirmed by CT, this will be considered PD.

If the positive FDG-PET scan during the study is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine whether there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET scan during the study corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this will not be considered PD.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

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Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

Appendix 7
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 8
Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance 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 housework or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 9
Substrates and Inhibitors of CYP Enzymes

The following drugs are sensitive substrates or substrates of CYPs 2C8, 2C9 and 2C19 with a low 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

Source: FDA draft guidance on "Drug Interaction Studies Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations," Feb 2012. Can be accessed from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf.