Official Title: An Open-Label, Phase I/II, Dose-Escalation Study Evaluating the Safety and Tolerability of GDC-0032 in Patients with Locally Advanced or Metastatic Solid Tumors or Non-Hodgkin's Lymphoma and in Combination with Endocrine Therapy in Patients With Locally Advanced or Metastatic Hormone Receptor-Positive Breast Cancer

NCT Number: NCT01296555

Document Date: Protocol Version A10: 12 July 2018

PROTOCOL

TITLE: **AN OPEN-LABEL, PHASE I/II, DOSE-ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF GDC-0032 IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS OR NON-HODGKIN'S LYMPHOMA AND IN COMBINATION WITH ENDOCRINE THERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC HORMONE RECEPTOR–POSITIVE BREAST CANCER**

PROTOCOL NUMBER:	PMT4979g (GO00886)
VERSION NUMBER	A10
EUDRACT NUMBER:	2012-002042-21
TEST PRODUCT:	GDC-0032
IND NUMBER:	110184
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	14 December 2010

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	12-Jul-2018 07:38:15

DATES AMENDED: Version A1: 15 August 2011
Version A2: 18 April 2012
Version A3: 30 October 2012 (Spain only)
Version A4: 7 March 2013
Version A5: 24 June 2013
Version A6: 16 December 2013
Version A7: 12 May 2014
Version A8: 31 March 2015
Version A9: 29 September 2016
Version A10: See electronic date stamp below.

PROTOCOL AMENDMENT VERSION A10:
RATIONALE

Protocol PMT4979g (GO00886) has been amended to reflect the Sponsor's decision to discontinue enrollment in the study as of 28 June 2018 and discontinue manufacturing of GDC-0032. This decision was based on results of the primary analysis of Study GO29058, a Phase III, double-blind study of GDC-0032 in combination with fulvestrant for the treatment of metastatic hormone receptor−positive breast cancer, which showed that GDC-0032 plus fulvestrant had modest clinical benefit and limited overall tolerability. Patients currently participating in the study as of 28 June 2018 will continue to receive treatment and undergo assessments as outlined in Appendix A-7 until 6 months after enrollment of the last patient (last patient in [LPI]+6 months). After this time, patients who are deriving clinical benefit from GDC-0032, as determined by the investigator, may continue their assigned treatment regimen until disease progression, unacceptable toxicity, expiration of the last batch of GDC-0032 (expected by May 2021), or discontinuation of the study by the Sponsor, whichever occurs first. Patients continuing treatment beyond LPI+6 months will undergo a reduced set of assessments, as outlined in a new schedule of assessments in Appendix A-9. The following sections have been updated to reflect these changes:

- Section 3.1 (Description of the Study)
- Section 4.5 (Study Assessments)
- Section 4.5.3 (Assessments during Treatment)
- Appendix A-7 (Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X [X1−X11] before LPI+6 Months)

New GDC-0032 adverse drug reactions were detected during the primary analysis for Study GO29058. The new adverse drug reactions have been added to Section 3.4.3, and management guidelines for infection have been added to Section 3.4.5.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, PHASE I/II, DOSE-ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF GDC-0032 IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS OR NON-HODGKIN'S LYMPHOMA AND IN COMBINATION WITH ENDOCRINE THERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC HORMONE RECEPTOR–POSITIVE BREAST CANCER**
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EUDRACT NUMBER:	2012-002042-21
TEST PRODUCT:	GDC-0032
IND NUMBER:	110184
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.

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

_____

Principal Investigator Name (print)

_____ _____

Principal Investigator Signature Date

Please retain the signed original of this form for your study files. Please return a copy to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, PHASE I/II, DOSE-ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF GDC-0032 IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS OR NON-HODGKIN'S LYMPHOMA AND IN COMBINATION WITH ENDOCRINE THERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC HORMONE RECEPTOR–POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	PMT4979g (GO00886)
VERSION NUMBER	A10
EUDRACT NUMBER:	2012-002042-21
TEST PRODUCT:	GDC-0032
PHASE:	I/II
INDICATION:	Advanced or Metastatic Solid Tumors
IND NUMBER:	110184
SPONSOR:	Genentech, Inc.

Objectives

Phase I Objectives (Stage 1 and Stage 2)

Phase I: Primary Objectives

The primary objectives of this study are the following:

- Stage 1: To evaluate the safety and tolerability of escalating doses of GDC-0032 administered daily for 28 days to patients with locally advanced or metastatic solid tumors.
- Stage 1: To determine the MTD of GDC-0032 and to characterize dose-limiting toxicities (DLTs) associated with GDC-0032 when administered daily for 28 days to patients with locally advanced or metastatic solid tumors
- To characterize the pharmacokinetic (PK) properties of GDC-0032
- To identify a recommended dose and schedule of single-agent GDC-0032 for future trials
- To evaluate the safety and tolerability of concomitant daily administration of GDC-0032 and letrozole in postmenopausal patients with locally advanced or metastatic hormone receptor–positive breast cancer
- To evaluate the safety and tolerability of concomitant administration of GDC-0032 and fulvestrant in postmenopausal patients with locally advanced or metastatic hormone receptor–positive breast cancer
- To evaluate the safety and tolerability of GDC-0032 in patients with non-Hodgkin's lymphoma
- To evaluate the safety and tolerability of GDC-0032 in patients with *PIK3CA*-mutant locally advanced or metastatic solid tumors

Phase I: Secondary Objectives

The secondary objectives of this study are the following:

- To make a preliminary assessment of the anti-tumor activity of single-agent GDC-0032 in patients with locally advanced or metastatic solid tumors, non-Hodgkin's lymphoma, tumors with *PIK3CA* mutations, HER2-positive breast tumors, and tumors with increased *PIK3CA* copy number

- To evaluate the effect of food on the pharmacokinetics of GDC-0032
- To evaluate the effect of GDC-0032 on the pharmacokinetics of midazolam
- To assess the pharmacokinetics of GDC-0032 and letrozole following administration of GDC-0032 in combination with letrozole
- To assess the pharmacokinetics of GDC-0032 and fulvestrant following administration of GDC-0032 in combination with fulvestrant
- To make a preliminary assessment of the anti-tumor activity of GDC-0032 in combination with letrozole in patients with locally advanced or metastatic hormone receptor–positive breast cancer
- To make a preliminary assessment of the anti-tumor activity of GDC-0032 in combination with fulvestrant in patients with locally advanced or metastatic hormone receptor–positive breast cancer

Phase I: Exploratory Objectives

The exploratory objectives of this study are the following:

- To determine the proportion of PI3K mutations, PI3K amplifications, and loss of PTEN expression in archival tissue and/or in circulating tumor DNA (ctDNA) and/or circulating tumor cells (CTCs) from blood obtained from patients in this study
- To make a preliminary assessment of PD, dose, and anti-tumor activity with PI3K mutation status, alterations determined by next-generation sequencing (NGS) platforms from archival and fresh tumor biopsies, DNA (ctDNA) and/or circulating tumor cells (CTCs), and patients' clinical and pathological characteristics
- To make a preliminary assessment of PD, dose, and anti-tumor activity with *PI3K* mutation status, BCL2 and MYC expression, *BCL2* and *MYC* rearrangement, cell-of-origin subtype, and DNA and RNA alterations determined by NGS in patients with relapsed or refractory DLBCL
- To evaluate changes in tumor ^{18}fluorodeoxyglucose (FDG) uptake as assessed by positron emission tomography (PET)
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to dose and anti-tumor activity
- To explore the potential role of polymorphisms in drug metabolism enzyme and transporter genes in the PK of GDC-0032
- To explore whether inhibition of PI3K results in changes in metabolic profiles in plasma and urine
- To obtain pharmacodynamic data on the effects of GDC-0032 in combination with letrozole on the PI3-kinase pathway using pre- and on-treatment biopsies

Phase II Objectives

Phase II: Primary Objective

The primary objective of the Phase II portion of the study is the following:

- To assess the clinical efficacy of the combination of GDC-0032 and fulvestrant, as measured by the clinical benefit rate and objective response rate, in all patients and patients with *PIK3CA*-mutant breast cancer

Phase II: Secondary Objectives

The secondary objectives of the Phase II portion of this study are the following:

- To assess the clinical efficacy of GDC-0032 and fulvestrant, as measured by duration of response, PFS, and OS in all patients and patients with *PIK3CA* mutant breast cancer
- To determine the nature, severity, and frequency of adverse events associated with the combination of GDC-0032 and fulvestrant

- To evaluate plasma concentrations of GDC-0032 and fulvestrant using a sparse sampling approach.

Phase II: Exploratory Objectives

The exploratory objectives of the Phase II portion of this study are the following:

- To explore the exposure-response relationship for safety and efficacy with GDC-0032 and fulvestrant
- To explore predictors of response to the combination of fulvestrant and GDC-0032 based on exploratory analyses of tumor tissue, circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and cytokine and chemokine levels from blood obtained from patients in this study

Study Design

Description of the Study

This is an open-label, multicenter, Phase I/II study. The Phase I portion is divided into two stages. Phase I, Stage 1 is a dose-escalation study using a 3 + 3 design to assess the safety, tolerability, and pharmacokinetics of GDC-0032 administered QD orally (PO) as a single agent. Phase I Stage 2 includes a cohort-expansion study to assess the safety, tolerability, pharmacokinetics, and preliminary activity of GDC-0032 administered as a single agent or in combination in multiple tumor types. In addition, Phase I Stage 2 Cohorts E and F are dose-escalation cohorts to assess GDC-0032 in combination with endocrine therapy in patients with hormone receptor–positive breast cancer. Alternate intermittent dosing schedules with GDC-0032 as either a single agent or in combination with endocrine therapy will also be evaluated in Stage 2. Patients enrolled in Phase I, Stage 1 and Stage 2 Cohorts A–G will receive GDC-0032 in capsule formulation, whereas patients in Phase I, Stage 2 Cohorts H–X will receive GDC-0032 in tablet formulation. See below for detailed descriptions of the individual cohorts.

The Phase II portion is an open-label, single-arm study to assess the clinical activity of GDC-0032 in capsule formulation administered QD orally in combination with fulvestrant.

Approximately 563–663 patients will be enrolled into Phase I of this study. Stage 1 (dose-escalation stage) of the Phase I portion of this study has completed enrollment with 34 patients enrolled. Stage 2 (cohort expansion stage) of Phase I will enroll approximately 529–629 patients with locally advanced or metastatic solid tumors or non-Hodgkin's lymphoma for which standard therapy either does not exist or has proven ineffective.

The Phase II portion of this study has completed enrollment with 60 postmenopausal patients with locally recurrent or metastatic hormone receptor–positive breast cancer enrolled.

All patients will be carefully followed for adverse events throughout the study, which will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0).

Patients will be enrolled at sites in the United States, Canada, and Europe.

The Sponsor has decided to discontinue enrollment in the study as of 28 June 2018 and discontinue manufacturing of GDC-0032. This decision was based on the results of the primary analysis of Study GO29058, a Phase III study of GDC-0032 in combination with fulvestrant for the treatment of metastatic, hormone receptor–positive breast cancer (GO29058), which showed that GDC-0032 plus fulvestrant had modest clinical benefit and limited overall tolerability. Patients participating in the study as of 28 June 2018 will continue to receive treatment and undergo assessments (as outlined in Appendix A-7) until 6 months after enrollment of the last patient (last patient in [LPI] +6 months). After this time, patients who are deriving clinical benefit from GDC-0032, as determined by the investigator, may continue their assigned treatment regimen until disease progression, unacceptable toxicity, expiration of the last batch of GDC-0032 (expected by May 2021), or discontinuation of the study by the Sponsor, whichever occurs first. Patients continuing treatment beyond LPI +6 months will undergo a reduced set of assessments, as outlined in Appendix A-9). Beyond LPI +6 months, discontinuation of GDC-0032 treatment will also

constitute discontinuation from the study. Survival follow-up will be halted as of LPI +6 months.

Phase 1

There are two stages to the Phase I portion of this study: Stage 1 (dose escalation) and Stage 2 (expansion). Each stage consists of three study periods: a screening period of 14 days or less, followed by a treatment period of up to 5 years, and a 30-day follow-up period.

Stage 1 will examine the safety and pharmacokinetics of increasing doses of GDC-0032 administered daily in a 28-day cycle in patients with locally advanced or metastatic solid tumors for which standard therapy either does not exist or has proven ineffective or intolerable. Thirty-four patients were enrolled in Stage 1, which has been completed. Refer to the Taselisib (GDC-0032) Investigator's Brochure for further information.

DLTs will be assessed during the DLT assessment window (Days 1–35 of Cycle 1 in Stage 1 and Days 1–28 in Stage 2, Cohorts E and F.

Stage 2 is designed to provide a preliminary assessment of single-agent activity with GDC-0032 and in combination with endocrine therapy to better characterize the safety, tolerability, and PD and PK variability of different doses and schedules for future studies. The pharmacokinetics and safety profile of GDC-0032 as a single-agent will be assessed in Cohorts A, B, C, D, G, H, T, T2, and X. The pharmacokinetics and safety profile of GDC-0032 in combination with letrozole will be assessed in Cohorts E, N, P, Q, R, and S. The pharmacokinetics and safety profile of GDC-0032 in combination with fulvestrant will be assessed in Cohorts F, J, K, L, and M.

Pharmacokinetics (PK): GDC-0032 pharmacokinetics will be evaluated in both stages. Changes to PK sampling times, slower dose escalation, and/or changes to the dosing schedule may be implemented on the basis of the results of PK analyses. Additional PK sampling may occur if GDC-0032 is held for an adverse event in order to better characterize the safety profile of GDC-0032.

Pharmacodynamics (PD): PD analyses will include imaging studies and assessments of PD biomarkers in both tumor tissue and blood:

Blood samples for platelet-rich plasma: In Stage 1 only, blood samples will be collected at various timepoints and processed to obtain platelet-rich plasma to explore changes in surrogate PD markers in response to GDC-0032.

Circulating tumor cells (CTC) analyses: Blood samples will be collected for analyses of CTCs from all patients pretreatment, on Day 15 or Day 16 of Cycle 1, on Day 1 of Cycle 3, at the study completion visit, and also at the clinic visit subsequent to a confirmed partial or complete tumor response (per Response Evaluation Criteria in Solid Tumors [RECIST]) for any patient, except for patients enrolled in Cohorts Q, R, S, T, T2, and X.

Circulating tumor DNA analysis: Blood samples for DNA sequencing to identify *PIK3CA* and cancer-related mutations in ctDNA will be collected from all patients pretreatment, Cycle 3 Day 1, Cycle 5 Day 1, at the study completion visit, and also at clinic visits on Day 1 of every odd-numbered cycle subsequent to a confirmed partial or complete tumor or lymphoma response for any patient.

Paired tumor biopsies: Optional paired tumor biopsy samples for patients in Stages 1 and 2 will be obtained pretreatment (prior to initiation of treatment with GDC-0032 on Day 1 of Cycle 1) and on-treatment during Cycle 1, between Days 15–21 (see Section 4.5.1.n). A tumor biopsy upon progression of disease will also be optional in this trial. From each of Cohorts N and P, a minimum of 3 patients with *PIK3CA*-mutant tumors and 3 patients with *PIK3CA*-wild-type tumors (12 total) are required to provide fresh pre-treatment and on-treatment (Cycle 1 Days 15–21, 1–4 hours post-GDC-0032 dose) biopsy samples to assess the effects of GDC-0032 on the PI3K (and other) pathways in the 2-mg and 4-mg tablet doses in combination with letrozole. In Cohort X3, a minimum of 5 patients are required to provide fresh pre-treatment and on-treatment biopsy samples to assess the effects of GDC-0032 on PI3K (and other cancer-related) pathways in HNSCC. If the tissue is not evaluable for these PD measurements, additional patients may be enrolled to complete the cohort.

FDG-PET imaging (includes FDG-PET and/or FDG-PET/CT scans) will be optional for patients in Phase I Stage 1, Cohort 1 but mandatory for patients in Stage 1, Cohorts ≥ 2 and in selected cohorts of Phase I Stage 2 (A-G, L, M, N, Q, R, and S). Patients will undergo FDG-PET imaging pretreatment (within 14 days before Cycle 1, Day 1), during the last week of Cycle 1 (e.g., between Days 29–35 [Stage 1] or Days 22–28 [Stage 2]), and at the end of Cycle 2 (between Days 22–28). If the pretreatment FDG-PET imaging for a patient shows no detectable tumor FDG uptake, then subsequent FDG-PET imaging will not be required for that patient. If there are no significant changes in FDG-PET in Cycle 1, FDG-PET imaging should not be obtained in Cycle 2. FDG-PET results will not be used for assessments of response or progression or for decisions regarding continuation of study treatment or study discontinuation, as FDG-PET has not been validated as an indicator of early response or progression in this setting.

Pharmacogenetic analysis: A blood sample for DNA isolation will be collected from all patients in this study for potential pharmacogenetic analysis of genes that may affect the pharmacokinetics of or response to GDC-0032.

Efficacy analysis: Disease status will be assessed using RECIST v1.1, except for Cohort T, which will use the Revised International Working Group (IWG) Response Criteria for Malignant Lymphoma and Cohort T2, which will use a modified version of the Lugano Response Criteria for Malignant Lymphoma. Patients will undergo tumor and response assessments at screening and then at the end of every even-numbered cycle (i.e., every two cycles), or earlier if clinically indicated. If a patient undergoes an interim tumor evaluation to confirm a partial response (i.e., between 4–7 weeks after previous tumor assessment), the next scheduled tumor assessment may be skipped so as to not expose patients to excessive radiation from tumor assessments.

In the absence of a DLT, unacceptable toxicity, or disease progression, patients with clinical benefit will be offered continued treatment with GDC-0032 for up to 5 years. Continued dosing beyond Cycle 1 will be at the discretion of the investigator, after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Patients who are benefiting from GDC-0032 after the 5-year treatment period may have the possibility of continued treatment, provided that study drug is available.

Patients who experience a DLT during the DLT Assessment Window (Days 1–35 of Cycle 1 for Stage 1 and Days 1–28 of Cycle 1 for Stage 2, Cohorts E and F), experience disease progression or unacceptable toxicity at any time during the study, or, in their opinion or the opinion of the investigator, are not benefiting from GDC-0032, will be discontinued from GDC-0032 study treatment. In some cases, if the adverse event is reversible and monitorable and the risk/benefit assessment suggests a reasonable rationale for continued treatment with study drug, patients may be allowed to continue with study treatment with agreement by the investigator and the Medical Monitor. A Study Completion/Early Termination Visit will be performed approximately 30 days after the last dose of GDC-0032. The end of the study is defined as the date on which the last patient has his or her last visit (LPLV).

Phase II

The Phase II portion of this study is designed to provide safety and efficacy data on the combination of fulvestrant and GDC-0032. Based on the Phase I (Stage 1 and Stage 2) clinical data, the recommended Phase II dose of GDC-0032 in combination with fulvestrant has been determined to be 6 mg QD.

In the Phase II portion of the study, approximately 60 postmenopausal patients with locally advanced or metastatic HER2-negative, hormone receptor–positive breast cancer who have not previously received fulvestrant will be enrolled in this study at sites in the United States and in Europe. A minimum of 30 patients will have *PIK3CA* mutant breast cancer.

All patients will be carefully followed for adverse events throughout the study, which will be graded according to NCI CTCAE v4.0.

GDC-0032 and fulvestrant plasma concentrations will be evaluated using a sparse sampling approach. Additional PK sampling may occur if GDC-0032 is held for an adverse event in order to better characterize the safety profile of GDC-0032.

PD analyses will include assessments of PD biomarkers in both tumor tissue and blood. Blood samples will be collected for analyses of CTCs, ctDNA, and cytokines and chemokines. Paired tumor biopsy samples obtained pretreatment (prior to initiation of treatment with GDC-0032 on Day 1 of Cycle 1) and during Cycle 2 will be optional for patients. A tumor biopsy upon progression of disease will also be optional.

Disease status will be assessed using RECIST v1.1. Patients will undergo tumor and response assessments at screening and then at timepoints as described in Appendix A-8, or earlier if clinically indicated. Bone scans will be performed as described in Appendix A-8.

All patients who discontinue from the treatment phase will be followed for survival information and subsequent anti-cancer therapies unless the patient requests to be withdrawn from study survival follow-up. Survival follow-up information will be collected via telephone calls, patient's medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by Genentech.

Length of Study

The enrollment duration is projected to be approximately 92 months after the first patient is enrolled.

End of Study

The end of the study is defined as the date on which the last patient has their last visit (LPLV). However, Genentech has the right to terminate this study at any time prior to the LPLV.

Outcome Measures

Safety Outcome Measures

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measure:

- Incidence of DLTs by NCI CTCAE v4.0 grade and associated dose of GDC-0032

In addition the safety will be assessed using the following secondary safety outcome measures:

- Incidence of adverse events by NCI CTCAE v4.0 grade and associated dose of GDC-0032
- Incidence of Grade 3 and 4 abnormalities in safety-related laboratory parameters and associated dose of GDC-0032

Pharmacokinetic Outcome Measures

The following primary PK parameters will be derived from the plasma concentration–time profile of GDC-0032, following administration of single and/or multiple doses, when appropriate as data allow:

- AUC_{inf} after single dose and $AUC_{0-\tau}$ after single and multiple doses
- Maximum plasma concentration (C_{max})
- Minimum plasma concentration (C_{min})
- Time to maximum plasma concentration (t_{max})
- Terminal half-life ($t_{1/2}$)
- Apparent clearance (CL/F) after single and multiple doses
- Accumulation ratio (AR) at steady-state

The following secondary PK parameters may also be derived, when appropriate as data allow:

- C_{max} and AUC under fed and fasted conditions (for patients participating in the food-effect assessment)
- AUC_{0-24hr}, C_{max}, t_{max}, and other PK parameters of midazolam, letrozole, and fulvestrant, when applicable

- Fraction of dose excreted (fe) and renal CL (CLr)
- PK-dose proportionality as assessed with C_{max} and AUC
- The time to achieve steady state as assessed with trough (predose) concentrations

For Phase II

A sparse sampling approach will be used to assess the plasma concentrations of GDC-0032 and fulvestrant following single and multiple doses.

Activity Outcome Measures

The following activity outcome measure will be assessed:

- Best overall response, duration of objective response, and progression-free survival (PFS) for patients with measurable disease according to RECIST v1.1
- In Cohort T, response assessment will be based on the 2007 Revised IWG Response Criteria in Malignant Lymphoma
- In Cohort T2, response assessment will be based on a modified version of the 2014 Lugano Response Criteria in Malignant Lymphoma.

Exploratory Outcome Measures

The following correlative biology outcome measures will be assessed:

- PET response for patients with detectable FDG tumor uptake at baseline
- Change from baseline in pAKT levels and/or other pathway biomarkers in platelet-rich plasma (Stage 1 only)
- Change in pS6 level as measured by IHC in patients with accessible tumors who provide consent for biopsy, and, if tissue quantity permits, change in expression or phosphorylation of other PI3-kinase pathway markers, and vascular markers, as measured by IHC and reverse phase protein array (RPPA)
- DNA mutation and copy number status of tumor type- and pathway-specific biomarkers (e.g., *PIK3CA*), RNA expression analysis, and PTEN expression in archival tumor tissue and/or in DNA from blood and in any fresh tumor biopsies obtained
- Enumeration of CTCs and assessment of PI3K and cancer biology pathway status, when appropriate, (e.g., *PIK3CA* mutation, PTEN expression, etc.) in CTCs and ctDNA from peripheral blood (Cohorts Q, R, S, T, T2, and X excluded from CTC analysis)
- Expression of cytokines and chemokines in plasma
- QT/QTc interval changes
- Tumor type–specific biomarkers as appropriate; examples may include BCL2 and MYC in DLBCL and p16 in HNSCC.

Investigational Medicinal Product

GDC-0032

GDC-0032 Drug Product is provided in a capsule formulation consisting of active pharmaceutical ingredient (API) powder (at different quantities) and hard gelatin capsule shells. The Drug Product will be initially provided as capsules of three strengths: 1 mg, 3 mg, and 5 mg. The 1-mg capsules are size 3 and Swedish orange, the 3-mg capsules are size 2 and white opaque, and the 5-mg capsules are size 2 and dark green. The only excipient in GDC-0032 Drug Product is the hard gelatin capsule shell.

The Drug Product is packaged in high-density polyethylene (HDPE) bottles. Each bottle is induction sealed and labeled for clinical use.

GDC-0032 capsules will be shipped to the study sites in bulk containers. GDC-0032 capsules should be stored at room temperature between 59–86°F (15–30°C) and should be protected

from light. Patients will be instructed to store study drug at room temperature between 59–86°F (15–30°C).

GDC-0032 is also provided for use in clinical studies as a white, film-coated, immediate-release tablet formulation of 2 mg strength. GDC-0032 tablets should not be stored above 25°C.

Patients with gastrostomy tubes who are unable to swallow tablets may receive their GDC-0032 dose in the form of a suspension prepared extemporaneously from (GDC-0032) 2-mg tablets. Patients will be provided with instructions for preparation of the suspension only at sites where administration of the extemporaneous suspension is approved by the Institutional Review Board/Ethics Committee.

Midazolam (Stage 2, Cohort C Only)

Refer to the midazolam Package Insert or SmPC for details on the formulation and storage of midazolam.

Letrozole (Stage 2, Cohorts E, N, P, Q, R, and S)

Refer to the letrozole (e.g., Femara®) package insert or SmPC for details on the formulation and storage of letrozole.

Fulvestrant (Stage 2, Cohorts F, J, K, L, and M; Phase II)

Fulvestrant is supplied in sterile single-patient prefilled syringes containing 50 mg/mL fulvestrant as a 5-mL injection. Refer to the fulvestrant (e.g., FASLODEX®) Package Insert or SmPC for details on the storage of fulvestrant.

Study Treatment

Dosage and Administration

The starting dose of GDC-0032 is 3 mg (capsule formulation) in the dose-escalation Phase I, Stage 1 portion.

On Day 1 of Cycle 1 for patients in Phase I, Stage 1 and Stage 2, Cohorts A–G, GDC-0032 will be administered to patients in a clinical setting that can accommodate frequent blood draws over a period of up to 72 hours after the morning dose is administered.

At each study visit, after establishing patient eligibility for continued administration of GDC-0032, a sufficient number of capsules or tablets should be dispensed to the patient to last only until the next visit or, at the investigator's discretion, through one cycle. Patients will self-administer GDC-0032 as detailed below, except on study visit days when the GDC-0032 will be administered in the clinic.

Patients will receive a single dose of GDC-0032 on scheduled dosing days. Patients will take GDC-0032 at the same time of day $\pm$ 2 hours, unless otherwise instructed. Patients will be instructed as to the number and strength of capsules or tablets to take, according to their assigned dose level and schedule. Patients with head and neck cancer and with gastrostomy tubes who are enrolled in Cohort X3 will be provided with special instructions on how to prepare a suspension (extemporaneous formulation) from GDC-0032 tablets for easier administration. To minimize the number of capsules or tablets administered, doses will be rounded so that a combination of no more than two different strengths will be required. The capsules should never be opened. Patients will be asked to record the time and date that they take each dose in a medication diary.

For Stage 1, unless otherwise instructed, GDC-0032 should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal), except on days of extensive PK sampling (Days 1 and 15 of Cycle 1) when administration will be under fasted conditions. For administration under fasted conditions, patients will fast overnight for at least 10 hours before dosing and 4 hours postdose and will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of GDC-0032 administration when the capsules will be swallowed whole (not chewed) with 240 mL (8 fluid ounces) of water.

For Stage 2 cohorts, GDC-0032 may be taken with or without food except on days on which there is a post-dose PK assessment where administration should be under fasted conditions. There is no water restriction around the time of GDC-0032 administration under fasted conditions for Stage 2 cohorts.

If a patient misses a GDC-0032 dose or vomits up a capsule or tablet, he or she should be instructed to skip that dose and to resume dosing with the next scheduled dose. Missed doses

will not be made up. Patients will be instructed to bring their medication diary to each study visit for assessment of compliance. Patients will also be instructed to bring all unused capsules or tablets to each study visit or, at the investigator's discretion, at the end of each cycle, for GDC-0032 accountability.

On safety assessment days, PK samples will be collected at the same time as other blood tests are performed, including fasting lipid panels. Patients will be instructed to hold the morning dose of GDC-0032 until after PK blood samples have been obtained. For Cohorts H–X, once fasting blood draws have been collected and GDC-0032 administered, the patient need not continue to remain fasted for any post-dose, PK blood draw.

Stage 1 Dosing

In Stage 1, Cycle 1 will be 35 days in length and will begin with a PK evaluation, during which all patients will receive a single fasting dose of GDC-0032 on Day 1 at their assigned dose level. The initial dose will be followed by a 7-day washout and frequent PK sampling up to 72 hours to determine the single-dose PK properties of GDC-0032 in humans. Urine samples will be collected up to 24 hours after the first dose to determine urinary elimination of GDC-0032. Blood samples will be taken at several scheduled timepoints to explore the surrogate PD response after a single dose. In Cycle 1, continuous GDC-0032 daily dosing will begin on Day 8 and will continue for 4 weeks (Days 8–35).

Subsequent cycles will be 28 days in length (4 weeks of daily dosing with GDC-0032).

Stage 2 Dosing

The dosing regimens for the Stage 2 cohorts are as follows:

- Cohort A: In Cycle 1, patients will receive a single dose of GDC-0032 on Day 1, and then daily doses from Day 8 to Day 35. On Day 1 or 8 of Cycle 1, GDC-0032 administration will be under either fasted or fed conditions for the food-effect assessment (i.e., fasted on Day 1 and fed on Day 8 or vice versa). Patients will fast overnight for at least 10 hours before the morning dose. If the patient is receiving a high-fat breakfast, the meal must be entirely consumed within $\leq$30 minutes and GDC-0032 dose will be given 30 minutes after the start of the meal. The high-fat meal (approximately 800 to 1000 calories) will consist of approximately 33 g protein, 58 g carbohydrate, and 75 g fat, respectively (e.g., 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash-brown potatoes, and 8 ounces of whole milk). Patients will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of 240 mL (8 fluid ounces) water intake required for administration of GDC-0032. GDC-0032 capsules will be swallowed whole (not chewed) with water. No additional food should be allowed for at least 4 hours postdose. In addition, patients will receive a GDC-0032 dose under fasted conditions on Cycle 1, Day 22 for assessment of steady state pharmacokinetics. Subsequent cycles will be 28 days in length (4 weeks of daily dosing with GDC-0032).
- Cohorts B, D, and G: In Cycle 1, patients will receive daily oral doses of GDC-0032 on an empty stomach (i.e.,1 hour before or 2 hours after a meal) on Days 1–28, except on Days 1, 8, and 15 when patients receive GDC-0032 under fasted conditions. For subsequent cycles patients will receive daily oral doses of GDC-0032 on Days 1–28.
- Cohort C: In Cycle 1, patients will receive midazolam 5 mg in hydrochloride syrup on Days 1 and 16. Each midazolam dose will be administered by oral syringe, followed by approximately 200 mL of water to rinse the mouth and swallow. Midazolam will not be mixed with any liquid before ingestion. Patients will then receive daily doses of GDC-0032 on Days 2–29. All doses will be taken on an empty stomach (i.e., 1 hour before or 2 hours after a meal), except on Days 1 and 16 when patients receive the doses under fasted conditions. For subsequent cycles patients will receive daily oral doses of GDC-0032 on Days 1–28.
- Cohort E: In Cycle 1, patients will receive daily oral doses of GDC-0032 and letrozole 2.5 mg orally on Days 1–28. Patients will take the GDC-0032 and letrozole doses on an empty stomach (i.e., 1 hour before or 2 hours after a meal), except on Days 1 and 15 when patients will receive the doses under fasted conditions. For subsequent cycles patients will continue to take daily oral doses of GDC-0032 and daily oral doses of letrozole 2.5 mg on Days 1–28. On study visit days, GDC-0032 and letrozole will be administered in the clinic.

- Cohort F: In Cycle 1, patients will receive daily oral doses of GDC-0032 on Days 1–28. Patients will take the GDC-0032 doses on an empty stomach (i.e., 1 hour before or 2 hours after a meal), except on Days 1 and 15 when patients will receive the doses under fasted conditions. Fulvestrant is supplied in sterile single-patient prefilled syringes containing a 250 mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–28 and will receive fulvestrant via intramuscular injections as described above in the clinic on Day 1 of each cycle.
- Cohort H: In Cycle 1, patients will receive daily oral doses of GDC-0032 on Days 1–21 of each 28-day cycle. For PK testing on Cycle 1 Day 15, patients will receive GDC-0032 under fasted conditions in the clinic. For subsequent cycles patients will receive daily oral doses of GDC-0032 on Days 1–21 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and fulvestrant have been administered, the patient need not continue to remain fasted until the 3hour post-dose PK blood draw.
- Cohort J: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–21. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. Fulvestrant will be supplied in sterile single-patient prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–21 of each cycle and will receive fulvestrant as described above in the clinic on Day 1 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and fulvestrant have been administered, the patient need not continue to remain fasted until the 3hour post-dose PK blood draw.
- Cohort K: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–5, 8–12, 15–19, and 22–26. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. Fulvestrant will be supplied in sterile single-patient prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–5, 8–12, 15–19, and 22–26 of each cycle and will receive fulvestrant as described above in the clinic on Day 1 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and fulvestrant have been administered, the patient need not continue to remain fasted until the 3-hour post-dose PK blood draw.
- Cohort L: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–7 and 15–21. For PK testing on Cycle 1 Day 1, patients will take GDC-0032 under fasted conditions in the clinic. Fulvestrant is supplied in sterile single-patient prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–7 and Days 15–21 of each cycle and will receive fulvestrant via intramuscular injections as described above in the clinic on Day 1 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and fulvestrant administered, the patient need not continue to remain fasted until the 3-hour post-dose PK blood draw.

- Cohort M: In Cycle 1, patients will receive a daily oral dose of 2 mg GDC-0032 in tablet form on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. Fulvestrant is supplied in sterile single-patient, prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1-2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles, patients will continue to receive daily oral doses of GDC-0032 on Days 1–28 and will receive fulvestrant via intramuscular injections, as described above, in the clinic on Day 1 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and fulvestrant have been administered, the patient need not continue to remain fasted until the 3-hour post-dose PK blood draw.
- Fulvestrant dosing exceptions (Cohorts F, J, K, L, and M): For patients with moderate hepatic impairment (Child-Pugh Class B), a single-agent dose of 250 mg is recommended on the basis of clinical data described in the fulvestrant package insert.
- Cohort N: In Cycle 1, patients will receive a daily oral dose of 2 mg GDC-0032 in tablet form and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 and letrozole doses under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily oral doses of GDC-0032 and daily oral doses of letrozole 2.5 mg on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 and letrozole will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and letrozole have been administered, the patient need not continue to remain fasted until the 3-hour post-dose PK blood draw.
- Cohort P: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 and letrozole under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily oral doses of GDC-0032 and daily oral doses of letrozole 2.5 mg on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 and letrozole will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and letrozole have been administered, the patient need not continue to remain fasted until the 3hour post-dose PK blood draw.
- Cohort Q: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–21 and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily oral doses of GDC-0032 on Days 1–21 and daily oral doses of letrozole 2.5 mg on Days 1–28. For PK testing on Day 1 of Cycle 2 and 6, GDC-0032 and letrozole will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and letrozole have been administered, the patient need not continue to remain fasted until the 3-hour post-dose PK blood draw.
- Cohort R: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–5, 8–12, 15–19, and 22–26 and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 and letrozole under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily oral doses of GDC-0032 on Days 1–5, 8–12, 15–19, and 22–26 of every cycle and daily oral doses of letrozole 2.5 mg on Days 1–28. For PK testing on Day 1 of Cycle 2 and 6, GDC-0032 and letrozole will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and letrozole have been administered, the patient need not continue to remain fasted until the 3-hour post-dose PK blood draw.
- Cohort S: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form on Days 1–7 and 15–21 and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 1, patients will take GDC-0032 and letrozole under fasted conditions in the clinic. For subsequent cycles, patients will continue to receive daily oral doses of GDC-0032 on Days 1–7 and Days 15–21 and daily oral doses of letrozole 2.5 mg orally on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 and letrozole will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 and letrozole have been administered, the patient need not continue to remain fasted until the 3-hour postdose PK blood draw.

- Cohort T: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take oral daily doses of GDC-0032 on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 has been administered, the patient need not continue to remain fasted until the 3-hour postdose PK blood draw.
- Cohort T2: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take oral daily doses of GDC-0032 on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 has been administered, the patient need not continue to remain fasted until the 3-hour post-dose PK blood draw.
- Cohort X, except sub-Cohort X3 patients who are taking GDC-0032 as suspension: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take oral daily doses of GDC-0032 on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 has been administered, the patient need not continue to remain fasted until the 3-hour postdose PK blood draw.
- Cohort X3: Patients with head and neck cancer who can swallow tablets will receive daily oral doses of 4 mg GDC-0032 in tablet form. For patients who cannot take tablets orally and have gastrostomy (G) tubes, GDC-0032 will be administered via G-tube as an aqueous suspension prepared extemporaneously from GDC-0032 tablets. Patients will be provided with special instructions on how to make a suspension from GDC-0032 tablets. The suspension is prepared by placing the GDC-0032 tablets in water (20 mL of water per tablet) in a glass container for 15 minutes at room temperature. The solution is then stirred or swirled to generate a suspension before administering into the G-tube, followed by two equivalent portions of water. Suspensions should be prepared immediately prior to dosing. Patients or caregivers should wash their hands after the preparation and any utensils used to prepare the suspension after administration. In Cycle 1, patients will receive daily doses of 4 mg GDC-0032 via G-tube on Days 1–28. Patients or caregivers should prepare GDC-0032 suspension under observation in the clinic on Cycle 1 Days 1 and 2. For PK testing, patients will take GDC-0032 on Cycle 1 Days 1 and 15 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily doses of GDC-0032 via G-tube on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. Once fasting blood draws have been collected and GDC-0032 has been administered, the patient need not continue to remain fasted until the 3-hour post-dose PK blood draw.

Phase II Dosing

In Cycle 1, patients will receive daily oral doses of GDC-0032 on Days 1–28. Patients will take the GDC-0032 doses on an empty stomach (i.e., 1 hour before or 2 hours after a meal), except on Days 1 and 15 when patients will receive the doses under fasted conditions. Fulvestrant will be supplied in sterile single-patient prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–28 and will receive fulvestrant as described above in the clinic on Day 1 of each cycle.

For patients with moderate hepatic impairment (Child-Pugh Class B), a single-agent dose of fulvestrant 250 mg is recommended based upon clinical data described in the fulvestrant package insert.

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 and the physician should be notified immediately.

Statistical Methods

Safety Analyses

Safety will be assessed through summaries of adverse events, changes in laboratory test results, and changes in vital signs. All patients who receive any amount of GDC-0032 will be included in the safety analyses.

GDC-0032 exposure, including the proportion of patients with dose modifications, will be summarized by assigned dose level and cohort.

All collected adverse event data will be listed by study site, patient number, and cycle. All adverse events occurring on or after treatment on Day 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. In addition, all serious adverse events, including deaths will be listed separately and summarized.

QT/QTc data will be analyzed using the E14 guidelines and may include analyses of central tendency, categorical analyses, analysis of the relationship between drug exposure and QT/QTc interval changes, and morphologic analyses of ECG waveforms.

Pharmacokinetic Analyses

Individual plasma GDC-0032 concentration vs. time data and summary statistics will be tabulated by dose level and schedule. Individual and mean (SD) plasma concentration versus time profiles will be plotted.

The plasma GDC-0032 pharmacokinetic data obtained after a single dose (Day 1) and at steady state (Day 15) will be analyzed using noncompartmental methods to estimate PK parameters, which include but are not limited to $AUC_{0-\tau}$ and/or AUC_{0-inf}, C_{max}, C_{min}, t_{max}, $t_{1/2}$, CL/F, accumulation (AR), renal excretion fraction (fe), urinary CL (CLr). Additional PK parameters may be determined as data allow. Estimates for these parameters and summary statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum) will be tabulated by dose level and schedule.

For Phase II, GDC-0032 and fulvestrant plasma concentrations will be tabulated from individual patients and presented with appropriate summary statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

Determination of Sample Size

A total of approximately 623–723 patients are expected to be enrolled in this study. In the single-agent dose-escalation portion of this study (Stage 1 of Phase I), 34 patients have been enrolled. Approximately 529–629 patients are expected to be enrolled in Stage 2 of Phase I, including with Amendment 8, 6 additional patients each in Cohorts N and P; 20 patients each in Cohorts Q, R, and S; 10 lymphoma patients in Cohort T; 10–20 patients with DLBCL in Cohort T2; 10–20 patients in each sub-cohort of the basket Cohort X (X1–X10); 20–40 patients in sub-Cohort X3; and 50 patients in sub-Cohort X11 with *PIK3CA*-mutant tumor types not covered in X1–X10. Phase II has fully enrolled with a total of 60 patients.

Stage 1: Dose Escalation

The sample size for Stage 1 is based on the dose-escalation rules described in the study design section of this protocol. The sample size for this trial is not based on explicit power or type I error considerations.

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in a given cohort of 6 patients is 46.9%, 26.5%, and 5.8%, respectively.

Stage 2: Expansion Cohorts

To better characterize the safety of single-agent GDC-0032 administered at the recommended dose for future studies, approximately 82 patients will be enrolled and treated with single-agent GDC-0032 in Stage 2, Cohorts A–D and G. For a given adverse event with a true rate of 10%, 5%, or 1% the probability of observing at least one such adverse event in 82 patients from the single-agent GDC-0032 expansion cohorts (Stage 2, Cohorts A–D and G) is >99.9%, 98.5%, and 56.1%, respectively.

Cohorts A–D and G–H of Stage 2 encompass distinct patient populations that may have differing safety profiles. For example, Cohort D includes HER2-positive metastatic breast cancer patients whereas Cohort G includes patients with solid tumors that have increased *PIK3CA* copy number.

Increasing the size of Cohorts A and B to 20 patients will provide more robust safety data in the patient populations tested. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in 20 patients is 87.8%, 64.1%, and 18.2%, respectively. Cohort H will also provide more robust safety data on a different single-agent schedule of GDC-0032 being given on a 21-day on, 7-day off (21/7) schedule. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in an expanded cohort of 40 patients is 98.6%, 87.1%, and 33.1%, respectively.

To better characterize the safety of the combination of GDC-0032 with either letrozole (Stage 2, Cohort E) or with fulvestrant (Stage 2, Cohort F), approximately 27–28 patients will be enrolled in each of these expansion cohorts. This number includes the possibility that two dose levels will be tested with 20 patients enrolled at the selected dose level.

Promising anti-tumor activity has been observed at the 6-mg QD capsule dose level of GDC-0032 in combination with letrozole (Cohort E) and in combination with fulvestrant (Cohort F). Several alternate dose schedules will be evaluated to obtain additional data on the relative tolerability of adding intermittent breaks to the GDC-0032 dosing schedule or lower doses of GDC-0032 in combination with either fulvestrant (Cohorts J, K, L, M) or letrozole (Cohorts N, P, Q, R, S).

Approximately 20 patients will be enrolled into Stage 2, Cohort J to evaluate an alternative dose schedule of GDC-0032 4-mg QD tablet dose level with a 21-day on, 7-day off (21/7) schedule in combination with fulvestrant.

Approximately 20 patients will be enrolled into Stage 2, Cohort K to evaluate an alternative dose schedule of GDC-0032 4-mg QD tablet dose level with a 5-day on, 2-day off (5/2) schedule in combination with fulvestrant.

Approximately 20 patients will be enrolled into Stage 2, Cohort L to evaluate an alternative dose schedule of GDC-0032 4-mg QD tablet dose level with a 7-day on, 7-day off (7/7) schedule in combination with fulvestrant.

Approximately 20 patients will be enrolled into Stage 2, Cohort M to evaluate an alternative dose level of GDC-0032 2-mg QD tablet dose level in combination with fulvestrant.

Approximately 26 patients will be enrolled into Stage 2, Cohort N to evaluate an alternative dose level of GDC-0032 2-mg QD tablet dose level in combination with letrozole. This includes six patient slots (three with *PIK3CA*-mutant and three with *PIK3CA*-wild-type tumors) in which paired pre- and on-treatment tumor biopsies are required.

Approximately 26 patients will be enrolled into Stage 2, Cohort P to evaluate an alternative dose level of GDC-0032 4-mg QD tablet dose level in combination with letrozole in a less heavily pretreated population as compared with Stage 2, Cohort E. This includes six patient slots (three with *PIK3CA*-mutant and three with *PIK3CA*-wild-type tumors) in which paired pre- and on-treatment tumor biopsies are required.

For the 12 slots in Cohorts N and P in which paired pre- and on-treatment tumor biopsies are required, if a patient enrolls in the study and either the pre- or the on-treatment biopsy tissue quality is deemed unevaluable by the Central Laboratory, the patient may continue on treatment, but additional patients may be enrolled to complete the cohort (at the Sponsor's discretion). The paired tumor biopsies support the exploratory objective of assessing GDC-0032 PD effects on the PI3K (and other) pathways. Therefore a limited number of patients (3 patients with *PIK3CA*-mutant and 3 patients with *PIK3CA*-wild type tumors in each cohort) was chosen to provide a preliminary PD assessment.

Approximately 20 patients will be enrolled into Stage 2, Cohort Q to evaluate an alternative dose schedule of GDC-0032 4-mg tablet dose level with a 21-day on, 7-day off (21/7) schedule in combination with letrozole.

Approximately 20 patients will be enrolled into Stage 2, Cohort R to evaluate an alternative dose schedule of GDC-0032 4-mg QD tablet dose level with a 5-day on, 2-day off (5/2) schedule in combination with letrozole.

Approximately 20 patients will be enrolled into Stage 2, Cohort S to evaluate an alternative dose schedule of GDC-0032 4 mg QD tablet dose level with a 7-day on, 7-day off (7/7) schedule in combination with letrozole.

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in an expanded cohort of 20 patients is 87.8%, 64.1%, and 18.2%, respectively. This is especially important in characterizing an adverse event such as pneumonitis that may occur at a low frequency. It is important to understand the safety profile of GDC-0032 in combination with letrozole as this regimen may be tested in future studies for patients with early hormone receptor–positive breast cancer, an indication with a unique risk-benefit profile. The combination of GDC-0032 and fulvestrant may be tested in future studies as an early-line therapy for patients with advanced hormone receptor–positive breast cancer.

In Cohort T, to characterize the safety and tolerability of single-agent GDC-0032 for patients with lymphoma, approximately 10 patients will be enrolled, irrespective of their tumor's *PIK3CA*-mutation status. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in an expanded cohort of 10 patients is 65.1%, 40.1%, and 9.6%, respectively.

In Cohort T2, to characterize the safety and tolerability of single-agent GDC-0032 for patients with DLBCL, approximately 10–20 patients will be enrolled, irrespective of their tumor's PIK3CA-mutation status. If less than 2 responders (CR or PR, confirmed or unconfirmed) are observed from the first 10 patients with DLBCL, enrollment will be suspended for Cohort T2; if 2 or more responders are observed from the first 10 patients, another 10 patients may be enrolled into the cohort. However, if clinical benefit is observed for the first 10 patients with DLBCL in Cohort T2 (e.g., a majority of patients demonstrate SD at Week 8 although there are less than 2 responders), then further enrollment of 10 additional patients may be allowed for this cohort, depending on the decision made by the Sponsor. Assessment for expansion of Cohort T2 will be made on a rolling basis, depending on when responses are observed.

In Cohort X (sub-Cohorts X1–X10), to provide preliminary efficacy and safety data of single agent GDC-0032 in a diverse population of patients with *PIK3CA*-mutant cancer, the following rule will be applied to each of the sub-cohorts: if less than 2 responders (CR or PR, confirmed or unconfirmed) are observed from the first 10 patients with *PIK3CA*-mutant cancer, enrollment will be suspended for that indication; if 2 or more responders are observed from the first 10 patients, another 10 patients will be enrolled into the cohort. However, if clinical benefit is observed for the first 10 patients with *PIK3CA*-mutant cancer in the cohort (e.g., a majority of patients demonstrate SD at Week 8 although there are less than 2 responders), then further enrollment of 10 additional patients may be allowed for this cohort, depending on the decision made by Genentech. Assessment for expansion of a given sub-cohort will be made on a rolling basis, depending on when responses are observed. These expansion rules will also be applied for the 10-20 patients with HNSCC with amplification of the PIK3CA gene number and no PIK3CA somatic mutations detected in Cohort X3. In addition, if a given indication is expanded to 20, a decision about further enrollment of additional patients beyond 20 (up to a maximum of 40 for any given indication, e.g., *PIK3CA*-mutant HNSCC) will be made by the Sponsor if clinical benefit is observed (e.g., $\geq$ 4 PR in 20 patients).

A positive *PIK3CA*-mutation or amplification status from local testing will be centrally confirmed for patients in Cohort X. If a patient enrolls as per a positive local test result and a mutation or amplification is not detected per central testing, the patient will be allowed to continue in the study, and additional patients may be enrolled to meet enrollment goals of patients with *PIK3CA*-mutant or amplified tumors.

With the assumption of an expected true response rate of 30% or higher, there is at most a 15% chance of observing less than 2 responses in 10 patients, which is the false negative rate. If the true response rate increases to 40%, the false negative rate decreases to 5%. Alternately, with the assumption of a response rate of 5% or less, there is at most a 9% chance of observing 2 or more responses in 10 patients, which is the false positive rate. If the response rate decreases to 4%, the false positive rate decreases to 6%.

Assuming a preferable response rate was observed ($\geq$ 20% responders) at Week 8 in Cohort T2 and X and 10 additional patients were enrolled, with an observed response rate of 20%, a sample size of 20 patients within a given indication (i.e., sub-Cohorts X1–X10) would result in

an 80% Pearson-Clopper exact CI of 9% to 36%, excluding a response rate of 8%. Assuming that the observed responder rate is 20% with 20 patients in a sub-cohort of Cohort X, and that an additional 20 patients were enrolled, the resulting sample size of 40 patients within a given indication would result in an 80% Pearson-Clopper exact CI of 12% to 30%, which is narrower than when the sample size is 20, thus providing more confidence in the observed response rate.

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in an expanded cohort of 20 patients is 87.8%, 64.2%, and 18.2%, respectively.

Phase II

The Phase II portion of the trial will evaluate safety and provide a preliminary evaluation of efficacy of the combination of GDC-0032 and fulvestrant as measured by ORR and CBR. The study is designed to estimate the ORR and the CBR with reasonable precision to contrast the results of this study with historical data from studies with fulvestrant in a similar patient population, which have ORR of 7%–10% and CBR rate of 32%–46% (Chia et al. 2008; Di Leo et al. 2010). CBR allows for evaluation of bone-only disease patients while ORR does not. Based upon previous literature, bone-only disease is approximately 30% of patients (Chia et al. 2008; Di Leo et al, 2010).

The Phase II portion of this trial will be able to detect a large benefit of the combination of GDC-0032 and fulvestrant, in terms of ORR. For example, an observed ORR of $\geq$30% in 21 patients with *PIK3CA*-mutant tumors (assuming 30% of the 30 patients will have non-measurable bone only disease) will have a 95% confidence interval of (14.6%, 57.0%), excluding an ORR of 10%. Similarly, an observed CBR of 67% in 30 patients will have a 95% confidence interval of (47.2%, 82.7%), excluding a CBR of 46%.

1. BACKGROUND

1.1 THE PHOSPHOINOSITIDE 3-KINASE PATHWAY

Phosphoinositide 3-kinase (PI3K) is a lipid kinase involved in tumor cell proliferation, survival, and migration upon activation by growth factor receptors and integrins. PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP_2) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP_3) (Cantley 2002), a second messenger involved in the phosphorylation of AKT and associated proteins in the AKT-mTOR pathway (Guertin and Sabatini 2007). Activating and transforming mutations, as well as amplification, in the p110α subunit of PI3K are commonly found in solid and hematological tumors. In addition, the PI3K-AKT pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling, the loss of the phosphatase tensin homolog (PTEN), or RAS mutations (Shayesteh et al. 1999; Cantley 2002; Massion et al. 2004; Wu et al. 2005).

GDC-0032 (also known as taselisib) is a potent, selective small molecule inhibitor of Class I PI3K-alpha, gamma, and delta isoforms that is being developed by Genentech, Inc. as an anti-cancer therapeutic agent. PI3K-AKT pathway activation has been implicated in several types of cancer (Cantley 2002, 2006; Ward et al. 2003). Activating and transforming mutations in the p110α subunit of PI3K are commonly found in tumors (Bachman et al. 2004; Samuels et al. 2004; Karakas et al. 2006). The beta isoform of PI3K is involved in glucose metabolism as evidenced by increased glucose levels in conditional p110β knockout mice compared with wild-type mice following a glucose challenge test (Jia et al. 2008). GDC-0032 has approximately 30-fold biochemical selectivity of the alpha isoform relative to the beta isoform and has been shown to be a potent inhibitor of growth in nonclinical models of PI3K-mutant tumors. GDC-0032 has higher potency against mutant p110α relative to wild-type and higher activity against *PIK3CA*-mutant cell lines and xenografts compared with non-*PIK3CA*-mutant models.

1.2 NONCLINICAL SUMMARY

A comprehensive nonclinical testing strategy was developed to investigate the pharmacology, pharmacokinetics, and toxicology of GDC-0032 and to enable the selection of a safe Phase I starting dose. The intended clinical route of administration for GDC-0032 is oral (PO). Thus, all pivotal in vivo nonclinical studies were conducted using PO administration.

Nonclinical studies of GDC-0032 demonstrate that GDC-0032 inhibits proliferation of p110α-mutant breast cancer cell lines and inhibits tumor growth in human breast xenograft models harboring the PI3K mutations. GDC-0032 treatment also substantially reduces levels of the PI3K pathway markers (pAKT, pPRAS40, and pS6). GDC-0032 has a favorable in vitro and nonclinical in vivo absorption, distribution, metabolism, and elimination profile that is characteristic of an orally administered compound that can achieve clinical exposure consistent with nonclinical efficacy findings described below. The results of the nonclinical toxicology program for GDC-0032 enabled the proposed

starting dose of 3 mg capsule formulation once daily (QD) for this study and support the evaluation of GDC-0032 as a potential therapeutic agent for cancer.

A summary of the key findings from nonclinical studies is presented below. See the GDC-0032 Investigator Brochure for additional details on the nonclinical studies.

1.2.1 Pharmacology

Extensive in vitro pharmacology studies were performed to characterize the inhibitory potency and selectivity of GDC-0032 for PI3K isoforms, and the effects of GDC-0032 on cell proliferation, cell cycle progression, and apoptosis. In vivo efficacy was assessed in nude and SCID mice with human tumor xenografts representing several types of cancer associated with PI3K pathway activation (i.e., PI3K mutation denoted as *PIK3CA*). In vitro and in vivo safety pharmacology studies were conducted to characterize potential effects on the cardiovascular system.

a. In Vitro Studies

In vitro studies characterizing the inhibitory potency and selectivity of GDC-0032 toward different PI3K isoforms and the effects of GDC-0032 on cell proliferation, cell cycle progression, and apoptosis in PI3K-mutant and PTEN-null cell lines were conducted. The following results were observed:

- GDC-0032 is a potent inhibitor of Class I PI3K alpha, delta, and gamma isoforms and a 30-fold less potent inhibitor of the beta isoform relative to the alpha isoform.
- GDC-0032 did not potently inhibit PIKK family enzyme DNA-PK. The 50% inhibitory concentration (IC_{50}) was $>$ 1000-fold more selective for the PIKK family kinases (C2 alpha, C2 beta, and VPS34 was $>$ 10 μM, 0.29 μM, and 0.39 μM, respectively), and other PIKK family kinases showed no significant inhibition at 1 μM.
- GDC-0032 inhibits cellular proliferation of KPL-4 and MCF7-neo/HER2 breast cancer (p110α-mutant) cell lines with mean IC_{50} values of 0.016 μM and 0.026 μM, respectively.

b. In Vivo Efficacy Studies

GDC-0032 inhibited tumor growth in nonclinical xenograft models of breast tumor cells harboring mutations in the p110α (H1047R) (KPL-4) or in the p110α E545K helical domain (MCF7-neo/HER2) following oral daily dosing. A pharmacodynamic (PD) and pharmacokinetic (PK) study in a KPL-4 xenograft tumor model was also conducted to correlate plasma levels of GDC-0032 with PD changes in the tumors. The following results were observed:

- Tumor growth was inhibited by an average of 105% at a maximum efficacious dose (MED) of 22.5 mg/kg QD (6 partial regressions out of 8 animals) in the MCF7-neo/HER2 breast xenograft model in nude mice. The 50% and 90% of maximal response (ED_{50} and ED_{90}) were determined to be 2.6 and 8.6 mg/kg, respectively, with a maximal response of 105% tumor growth inhibition (TGI) observed in the highest dose group of 22.5 mg/kg.

- Tumor growth was inhibited by an average of 128% at an MED of 25 mg/kg QD (7 partial regressions and 1 complete regression out of 8 animals) in the KPL-4 human breast xenograft model in SCID beige mice. The ED_{50} and ED_{90} (defined as the 50% and 90% of maximal response) were determined to be 0.8 and 14.1 mg/kg, respectively, with a maximal response of 128% TGI observed in the highest dose group of 25 mg/kg
- PI3K pathway markers phosphorylated AKT (pAKT), phosphorylated PRAS40 (pPRAS40), and phosphorylated S6 (pS6) were reduced for up to 24 hours in response to a single dose of GDC-0032, and substantial reduction of pathway markers was associated with plasma levels $>$ 2.7 μM in the KPL4 breast cancer xenograft model

1.2.2 Pharmacokinetics

In vitro studies were performed to determine the disposition of GDC-0032, to investigate its metabolism in various species, and to assess its potential for drug-drug interaction (DDI). PK studies were performed in mice, rats, dogs, and monkeys and toxicokinetic (TK) evaluations were performed in rats and dogs as part of the GLP toxicity studies. These studies were conducted to provide information on the nonclinical pharmacokinetics or toxicokinetics of GDC-0032, to support the interpretation of toxicology studies and to aid in the selection of the appropriate starting dose for use in clinical trials. Human PK parameters and exposure were predicted and the potential for DDI was also evaluated. However, the definitive assessment for DDI potential will be based on concentrations achieved in clinical studies.

a. In Vitro Studies

- Plasma protein binding was moderate to high, ranging from 70.7% to 97.6% (mouse, rat, rabbit, monkey, dog, and human plasma). Binding to 1 mg/mL of human alpha-1 acid glycoprotein and 40 mg/mL human serum albumin ranged from 45.0 to 58.3% and 64.7 to 67.3%, respectively.
- No human-specific metabolites of GDC-0032 (10 μM) were detected in the in vitro metabolism studies conducted in rat, dog and human hepatocytes.
- GDC-0032 was primarily metabolized by CYP3A4 in human liver microsomes via oxidation at the core of the molecule or hydrolysis of the amide group. The formation of the main metabolite (M3) appeared to be principally mediated by CYP3A4, which was confirmed by incubation of 1 μM GDC-0032 with human recombinant cytochrome P450 (CYP).
- In vitro CYP inhibition studies in human liver microsomes and induction studies in human hepatocytes suggest a low-to-moderate potential for DDI. GDC-0032 appeared to be a weak time-dependent inhibitor of CYP3A4, with K_I and k_{inact} values of 77 μM and 0.030 min^{-1}, respectively, when testosterone was used as the probe substrate. In cryopreserved human hepatocytes, the mean percent activity of CYP3A4/5 compared to vehicle control increased nearly 2- and over 3-fold following incubation with 0.1 μM and 1 μM GDC-0032, respectively. At these concentrations, the level of enzyme induction was $<$ 31% of the positive control rifampicin at 25 μM.

b. In Vivo Studies

- GDC-0032 has low plasma clearance in mice, rats, and monkeys of 2.73, 1.77, and 4.15 mL/min/kg, respectively, and moderate clearance of 10.1 mL/min/kg in dogs after intravenous (IV) administration. Renal clearance in monkeys and dogs was negligible, accounting for less than 1% of plasma clearance.
- Terminal half-life ranged from 1.87 hours in mice to 4.42 hours in dogs.
- The volume of distribution at steady-state (V_{ss}) ranged from approximately 41% of total body water volume in the rat, to 4-fold total body water volume in the dog.
- Bioavailability following oral administration ranged from 41.5% to 117% in nonclinical species tested.
- In the 28-day GLP rat toxicity study, the increases in maximum concentration observed (C_{max}) and area under the concentration–time curve from Time 0 to last measurable concentration ($AUC_{0\text{-tlast}}$) were generally greater than dose-proportional on Day 1, and generally less than dose-proportional on Day 28. The plasma concentrations of GDC-0032 were higher on Day 28 than on Day 1 at the 0.3 mg/kg dose level and lower on Day 28 than on Day 1 at the 3 mg/kg dose. The $AUC_{0\text{-tlast}}$ at the highest dose of 3 mg/kg on Day 28 was 16400 ng • mL/hour (35.6 μM • hour), with a corresponding C_{max} of 1960 ng • mL (4.3 μM).
- In the 28-day GLP dog toxicity study, exposure (C_{max} and $AUC_{0\text{-tlast}}$) increased in a dose-proportional manner in the 28-day toxicity and TK study in dogs given GDC-0032 QD, and exposure was generally higher on Day 28 than on Day 1. The $AUC_{0\text{-tlast}}$ at the mid-dose of 0.3 mg/kg on Day 28 was 294 ng• hour/mL (0.64 μM • hour), with a corresponding C_{max} of 47.5 ng/mL (0.1 μM).
- No apparent sex differences were observed in GDC-0032 mean C_{max} and $AUC_{0\text{-tlast}}$ values for rats or dogs.

c. Human Pharmacokinetic Predictions

Allometric scaling was performed to predict clearance and volume of distribution of GDC-0032 in humans. Estimates of clearance and volume of distribution from nonclinical PK studies were used to predict these parameters in humans. Human clearance (CL) was predicted to be 10 and 3.1 mL/min/kg using the simple allometric scaling method and the maximum lifespan potential (MLP) correction, respectively (as proposed by the “rule of exponents”; Mahmood and Balian 1996). Predicted volume of distribution was 3.9 L/kg in humans. Using a CL of 3.1 mL/min/kg, an absorption rate constant (ka) derived from dog PK, and an assumed bioavailability of 85%, simulations based on a one-compartment model predicted an AUC of approximately 193 ng • hour/mL (0.4 μM • hour) and a C_{max} of 11 ng/mL (0.02 μM) at the proposed starting dose of 3-mg capsule formulation in humans.

1.2.3 Toxicology

The toxicology program was designed to evaluate the toxicity profile of GDC-0032, enable selection of a safe starting dose for the Phase I trial, and support QD oral dose administration of GDC-0032 for up to 28 days to cancer patients in clinical trials. Rats

and dogs were chosen as appropriate species for toxicology studies on the basis of metabolic profiles similar to humans in in vitro assays.

Nonclinical findings were consistent with the anticipated pharmacologic effects of PI3K inhibition and include effects on glucose metabolism and manifestations of lymphoid depletion in tissues and effects on bone marrow (see Section 3.4.1). Additional nonclinical findings included reversible effects on body weights in rats (decreased body weight gain) and in dogs (body weight loss), reversible microscopic formation of cysts in ovaries of rats, and reversible GI inflammation in dogs administered GDC-0032. The majority of findings was minimal to mild, reversible, and considered not adverse. Moreover, these findings are expected to be clinically monitorable (except for microscopic ovarian cysts) and manageable in patients. The severely toxic dose to 10% of animals (STD_{10}) in rats was 3 mg/kg and the highest non-severely toxic dose (HNSTD) in dogs was 0.3 mg/kg when GDC-0032 was given QD PO for 28 days. The rat STD_{10} enabled a safe clinical start dose of 3 mg QD in patients. The results from the toxicology studies provide a robust characterization of the safety profile of GDC-0032 and support the administration of GDC-0032 to cancer patients for up to 28 daily doses in the proposed Phase I trial.

The maximum recommended starting dosage (MRSD) of 3-mg capsule QD for this Phase I trial was calculated after evaluation of all the relevant toxicity data and is aligned with current regulatory guidance (DeGeorge et al. 1998; U.S. FDA 2002; ICH S9 2010).

The STD_{10} in rats was determined to be 3 mg/kg QD (18 mg/m^2 QD), and one-tenth of the rat STD_{10} in dogs, on an mg/m^2 basis, was not severely toxic to dogs; the rat toxicity data formed the basis for the MRSD calculation. A rat-to-human body surface area (BSA) conversion factor of 0.16 and a safety factor of 10 were applied to the STD_{10} in rats and the resulting MRSD is 0.05 mg/kg or 3 mg QD per 60-kg patient.

At the MRSD of 3 mg QD, the human AUC and C_{max} are projected to be 0.4 μM • hour (193 ng • hour/mL) and 0.02 μM (11 ng/mL), respectively, on the basis of human PK parameters predicted by allometric scaling (MLP scaling) (Mahmood and Balian 1996). These values are approximately 89-fold and 215-fold lower, respectively, than the AUC and C_{max} observed in rats at the STD_{10} and 1.5-fold and 5-fold lower, respectively, than the AUC and C_{max} in dogs at the HNSTD.

1.3 SUMMARY OF CLINICAL DATA FOR GDC-0032

1.3.1 Clinical Safety Data with GDC-0032

As of 30 July 2014, 230 patients have been treated with GDC-0032 in the Phase I/II Study PMT4979g, either as single-agent (n = 115), in combination with fulvestrant (n = 87), or in combination with letrozole (n = 28).

As of 30 July 2014, enrollment into the single-agent dose-escalation stage of Study PMT4979g was completed, with 34 patients enrolled at GDC-0032 doses ranging

from 3- to 16-mg capsules daily. GDC-0032 was well-tolerated in the first three cohorts (3, 5, and 8 mg), with no patients experiencing a dose-limiting toxicity (DLT). At the 16-mg dose level, 2 of the 11 safety-evaluable patients experienced a DLT (Grade 4 hyperglycemia and Grade 3 fatigue). At the 12-mg dose level, 1 of the 10 safety-evaluable patients experienced a DLT of Grade 3 acute renal failure. The maximum administered dose was 16 mg. Although the single-agent GDC-0032 maximum tolerated dose (MTD) was not exceeded at the 16-mg dose level, on the basis of long-term safety data and observed anti-tumor activity through multiple treatment cycles, the recommended single-agent dose and schedule for the single-agent GDC-0032 capsule expansion stage is 9 mg QD. In the single-agent expansion cohorts in Stage 2, 77 patients have been treated with GDC-0032 9-mg capsules in Cohorts A–D and G.

An equivalent dose conversion between capsules and tablets was developed (see Section 1.3.2). Four patients have been treated with GDC-0032 6-mg tablet (equivalent to 9-mg capsule) in Cohort H. In Cohort H, patients receive GDC-0032 tablets on a 21-day-on, 7-day-off (21/7) intermittent schedule. In addition, lower doses (2 and 4 mg) of GDC-0032 tablets are being investigated as a single agent, in combination, and in different dosing schedules.

As of 30 July 2014, adverse events of any grade that occurred in $\geq$ 10% of the 115 patients treated with single-agent GDC-0032 and assessed by the investigator as related to GDC-0032 were diarrhea (52%), hyperglycemia (35%), nausea (35%), fatigue (31%), decreased appetite (25%), rash (18%), stomatitis (15%), vomiting (13%), and mucosal inflammation (12%). Among the 115 patients treated with single-agent GDC-0032, at least one Grade $\geq$ 3 adverse event was reported for 72 patients (63%). Grade 3 or higher adverse events reported for $>$ 1 patient were hyperglycemia (14%), colitis (6%), diarrhea (5%), hypokalemia (5%), pneumonitis (5%), anemia (4%), fatigue (4%), rash (4%), abdominal pain (4%), increased ALT (3%), dyspnea (3%), hyponatremia (3%), hypophosphatemia (3%), increased lipase (3%), pneumonia (3%), urinary tract infection (3%), congestive cardiac failure (2%), Clostridium difficile infection (2%), hypoxia (2%), neutropenia (2%), pruritus (2%), respiratory failure (2%), and stomatitis (2%).

As of 30 July 2014, adverse events of any grade that occurred in $\geq$ 10% of the 87 patients treated with GDC-0032 plus fulvestrant and assessed by the investigator as related to GDC-0032 were diarrhea (64%), nausea (32%), fatigue (28%), decreased appetite (25%), mucosal inflammation (21%), rash (21%), asthenia (18%), hyperglycemia (17%), colitis (16%), stomatitis (16%), dry skin (13%), dyspepsia (12%), and dysgeusia (10%).

Among the 87 patients treated with GDC-0032 and fulvestrant, at least one Grade 3 or higher adverse event was reported for 42 patients (48%). Grade 3 or higher adverse events reported for $>$ 1 patient were colitis (12%), diarrhea (10%), hyperglycemia (9%),

rash (5%), increased AST (3%), hypokalemia (3%), hyponatremia (3%), anemia (2%), ascites (2%), back pain (2%), mucosal inflammation (2%), and pneumonia (2%).

As of 30 July, 2014, adverse events of any grade that occurred in ≥ 10% of the 28 patients treated with GDC-0032 plus letrozole and were assessed by the investigator as related to GDC-0032 were diarrhea (68%), stomatitis (39%), nausea (36%), fatigue (29%), rash (29%), decreased appetite (25%), hyperglycemia (25%), dysgeusia (21%), mucosal inflammation (21%), vomiting (21%), dry skin (18%), muscle spasms (18%), asthenia (14%), dry mouth (14%), pruritus (14%), and AST increased (11%).

Among the 28 patients treated with GDC-0032 and letrozole, at least one Grade 3 or higher adverse event was reported for 20 patients (71%). Grade 3 or higher adverse events reported for > 1 patient were diarrhea (14%), asthenia (7%), increased blood alkaline phosphatase (7%), hyperglycemia (7%), hypokalemia (7%), mucosal inflammation (7%), and stomatitis (7%).

Refer to the Taselisib (GDC-0032) Investigator's Brochure for further details.

1.3.2 Preliminary Pharmacokinetics

The pharmacokinetics of GDC-0032 have been characterized following administration of 3-, 5-, 8-, 12-, and 16-mg QD capsule doses during the Stage 1 dose-escalation portion of this study. The cohort mean apparent clearance (CL/F) and the terminal half life ($t_{1/2}$) following a single oral dose of GDC-0032 had a range of 4.77–9.17 L/hour and 37.2–43.8 hours, respectively. Following daily oral dosing for 8 days, there was a 2- to 4-fold accumulation of GDC-0032. The pharmacokinetics of GDC-0032 were approximately dose proportional and time independent. Preliminary PK data from Cohorts E and F suggest that GDC-0032 does not appear to cause or to be a target (neither victim nor perpetrator) of a drug-drug interaction with fulvestrant or letrozole.

GDC-0032 was metabolized primarily by CYP3A4 in human liver microsomes and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low to moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a DDI.

The impact of formulation on the pharmacokinetics of GDC-0032 has been assessed in Study GP28619 in healthy volunteers. The relative bioavailability of a 3-mg GDC-0032 tablet versus 3-mg capsule formulation was 152% (90% CI: 142%, 163%) for GDC-0032 AUC and 196% (90% CI: 177%, 217%) for GDC-0032 C_{max}. In the same study, the 2-mg GDC-0032 tablet demonstrated pharmacokinetics comparable to the 3-mg capsule dose. Relative bioavailability of a 2-mg tablet versus a 3-mg capsule was 101% (90% CI: 94.8%, 107%) for AUC and 117% (90% CI: 106%, 128%) for C_{max}. A 4-mg GDC-0032

tablet dose is estimated to provide an AUC equivalent to that of a 6-mg capsule dose because of the ability of GDC-0032 to demonstrate linear, dose-proportional pharmacokinetics over a broad dose-range.

The drug exposure (AUC) for GDC-0032 in a healthy volunteer study (Study GP28619) was minimally affected by the consumption of a high-fat meal. Therefore, GDC-0032 may be taken without regard to the timing of the administration of food.

For additional details, refer to the GDC-0032 Investigator's Brochure.

1.3.3 Preliminary Pharmacodynamics

Paired tumor biopsy samples were obtained from a patient with non–small cell lung cancer (NSCLC) treated at the 3-mg GDC-0032 dose level at screening (pretreatment biopsy) and during Cycle 1 in Study PMT4979g (on-treatment biopsy). Inhibition of PI3K pathway markers, including decreases of $>60\%$ in pAKT and pS6 (compared with baseline), were demonstrated in this patient's paired tumor biopsy samples.

For additional details, refer to the GDC-0032 Investigator's Brochure.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.4.1 Rationale for Phase I

The PI3K pathway has been implicated in cancer by several important mechanisms in human tumors. It is a key pathway that is activated by upstream receptor tyrosine kinases that are known to stimulate cancer cell proliferation, such as human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), and insulin-like growth factor 1 receptor (IGF-1R). Activating mutations, as well as amplification, in the p110α subunit of PI3K have been identified in many tumor types (Shayesteh et al. 1999; Bachman et al. 2004; Massion et al. 2004; Samuels et al. 2004; Wu et al. 2005). These activating mutations have demonstrated promotion of growth and invasion in cancer cells that is abrogated by PI3K inhibitors. The pathway is constitutively activated by the loss of the tumor suppressor PTEN, a phosphatase that counteracts the kinase activity of PI3K, in many tumor types (Li et al. 1997; Steck et al. 1997). AKT, which is directly downstream of PI3K, has also been shown to be overexpressed in some tumor types (Staal 1987; Cheng et al. 1992; Bellacosa et al. 1995) and to be transforming (Aoki et al. 1998). Further downstream, PI3K activity leads to the phosphorylation and activation of mammalian target of rapamycin (mTOR), and mTOR inhibitors have already demonstrated some efficacy in cancer patients (Hudes et al. 2007).

Activation of the PI3K–AKT pathway, which promotes proliferation and invasive activity of cancer cells, is abrogated by PI3K inhibitors. The beta isoform of PI3K is involved in glucose metabolism as evidenced by increased glucose levels in conditional p110β knockout mice compared with wild-type mice following a glucose challenge test (Jia et al. 2008). These data provide a strong rationale for developing beta

isoform-sparing PI3K inhibitors that inhibit the PI3K pathway in human tumors while minimizing effects on glucose metabolism.

The Phase I portion of this study is composed of two stages. The open-label, first-in-human, Phase I, dose-escalation portion (Stage 1) is designed to define the safety profile and PK and PD characteristics of GDC-0032 QD in patients with locally advanced or metastatic solid tumors for which standard therapy either does not exist or has proven ineffective or intolerable. In Phase I, Stage 2, several expansion cohorts have been added to define the safety profile and PK and PD characteristics of GDC-0032 alone or in combination in various patient populations.

1.4.1.1 Rationale for Phase I Stage 2 Cohorts E, F, J, K, L, M, N, P, Q, R, and S: GDC-0032 in Combination with Letrozole or Fulvestrant in Hormone Receptor–Positive HER2-Negative Breast Cancer

The PI3K pathway is often activated in hormone receptor–positive breast tumors. A confirmed partial response has also been observed in a patient with hormone receptor–positive, HER2-positive, *PIK3CA*-mutant breast cancer in Stage 1 Cohort 2 treated at the 5-mg capsule daily dose of GDC-0032 that was well tolerated. On the basis of the strong scientific rationale and preliminary clinical data for GDC-0032 in hormone receptor–positive breast cancer, the combination of GDC-0032 and the aromatase inhibitor letrozole will be evaluated in postmenopausal patients with hormone receptor–positive metastatic breast cancer to obtain data on the safety profile and pharmacokinetics of the combination. The combination of GDC-0032 and the estrogen receptor antagonist fulvestrant will also be evaluated in postmenopausal patients with hormone receptor–positive metastatic breast cancer to obtain data on the safety profile and pharmacokinetics of the combination. It is important to test both combinations as letrozole and fulvestrant have different mechanisms of action, different pharmacokinetic properties, and different potential for DDI with GDC-0032. Additional cohorts have been added to investigate different dosing schedules of GDC-0032 in combination with fulvestrant or letrozole.

Preliminary efficacy results from the endocrine therapy combination Stage 2 Cohorts E (with letrozole) and F (with fulvestrant) have demonstrated that some patients who started at the GDC-0032 6-mg QD capsule dose and then dose-reduced to 3-mg QD capsule have been able to maintain partial responses. Therefore, several alternate dose schedules and dose levels will be tested to obtain further data on the relative tolerability of adding intermittent breaks to the GDC-0032 dosing schedule and a lower continuous GDC-0032 dosing with endocrine therapy. Data from prior studies with other PI3K inhibitors suggest that adding intermittent breaks may help decrease toxicities while maintaining an equivalent amount of anti-tumor activity (Mayer et al. 2012).

1.4.1.2 Rationale for Phase I Stage 2 Cohort T: GDC-0032 Single Agent in Non-Hodgkin's Lymphoma

The PI3K pathway is activated in both normal and malignant B-cells, with the PI3K-delta isoform playing an important role. Inhibition of PI3K-delta with idelalisib has shown clinical activity in chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and small cell lymphocytic lymphoma (SLL) (Miller et al. 2015). GDC-0032 is a very potent PI3K-delta inhibitor in addition to a potent inhibitor of alpha and gamma isoforms and thus may provide clinical benefit in patients with hematologic malignancies. For example, resistance to a delta-selective PI3K inhibitor in mantle cell lymphoma can occur through activation of p110α, and therefore, the addition of alpha inhibition may provide benefit (Iyengar et al. 2013). Nonclinical data show that GDC-0032 is more potent than idelalisib against CD20+ lymphoma cell lines in vitro and delays tumor growth in a xenograft model in vivo (Genentech internal data). On the basis of these promising nonclinical data and the demonstrated clinical efficacy of PI3K-delta inhibition, the study was expanded in Amendment 8 to add Cohort T in which patients with relapsed and refractory non-Hodgkin's lymphomas will be enrolled to receive GDC-0032 6-mg tablet QD as a single agent. In Amendment 9, the starting dose in Cohort T is changed to 4-mg tablet QD (see Section 3.2.31 for rationale).

1.4.1.3 Rationale for Phase I Stage 2 Cohort T2: GDC-0032 Single Agent in Diffuse Large B-Cell Lymphoma

Cohort T was added to the study in Amendment 8 to examine safety and preliminary efficacy of GDC-0032 in patients with relapsed and/or refractory non-Hodgkin's lymphoma. A PET complete metabolic response was observed in a patient with diffuse large B-cell lymphoma (DLBCL), and partial responses were observed in a patient with follicular lymphoma and in a patient with MALT lymphoma, among 8 patients enrolled in Cohort T as of 18 March 2016. To better understand the safety, tolerability, and preliminary efficacy of GDC-0032 in DLBCL, the study has been amended to add Cohort T2 in which patients with relapsed and/or refractory DLBCL will be enrolled to receive GDC-0032 4-mg tablet QD as a single agent. Recruitment into Cohort T2 may be expanded from 10 to a total of approximately 20 patients if a $\geq$20% response rate has been demonstrated in the first 10 patients with an acceptable safety profile. If further clinical benefit is observed, additional enrollment may be allowed (see Section 4.9.10).

1.4.1.4 Rationale for Phase I Stage 2 Cohort X: "Basket Cohort"

Data from patients treated with GDC-0032 indicated enhanced activity in tumors harboring mutations in *PIK3CA*. Preliminary evidence from the dose-escalation portion of Study PMT4979g suggests that GDC-0032 has activity across multiple tumor types with *PIK3CA* mutations, including breast, lung, gynecologic, and head and neck (see Section 3.2.7). On the basis of the prevalence rate of *PIK3CA* mutations in these cancers and to further identify other cancers in which GDC-0032 may have activity, the study has been amended to add Cohort X in which patients with *PIK3CA*-mutant cancers will be enrolled to receive GDC-0032 6-mg tablet QD as a single agent.

This basket cohort design will comprise 11 sub-cohorts representing different tumor types. Patients are required to have *PIK3CA*-mutant–positive tumors for enrollment. Because the prevalence of the *PIK3CA* mutation is widespread across multiple tumor types but of variable prevalence in each tumor type, a basket design would be the most efficient approach to evaluate GDC-0032 in patients with *PIK3CA*-mutant tumors based on local or central assessment. For example, in patients with endometrial cancer, data from The Cancer Genome Atlas Research Network (2013) showed 53% of a total of 232 cases had mutant *PIK3CA*. In one study of 109 cases of urothelial carcinoma of the bladder, 21% had mutant *PIK3CA* (Kim et al. 2014). In patients with head and neck squamous-cell cancer (HNSCC), data from The Cancer Genome Atlas Research Network (2015) showed 21% of a total of 279 cases had mutant *PIK3CA*. In other tumor types represented in Cohort X, the incidence of *PIK3CA* mutation had a range of 5%–22% in data from The Cancer Genome Atlas.

PIK3CA amplification is a common genetic alteration in HNSCC and can occur independently of *PIK3CA* point mutations in these patients. Nonclinical data indicate that GDC-0032 has activity in *PIK3CA*-amplified HNSCC cell lines (Zumsteg et al. 2016). To better understand the safety, tolerability, and preliminary efficacy of GDC-0032 in patients with HNSCC with amplification of the *PIK3CA* gene and no *PIK3CA* somatic mutations detected, the study has been amended in Amendment 9 to add 10–20 of these patients in Cohort X3. Refer to the laboratory manual for definition of *PIK3CA* amplification.

Recruitment into a sub-cohort or indication may be expanded to a total of 20 patients if a ≥ 20% response rate has been demonstrated in the first 10 patients in that particular sub-cohort. If further clinical benefit is observed, additional enrollment may be allowed (see Section 4.9.10). These cohorts will evaluate preliminary safety and efficacy and inform whether patients with *PIK3CA* mutations will benefit from treatment with GDC-0032.

1.4.2 Rationale for Phase II

In order to obtain more information on the long-term tolerability and efficacy of GDC-0032 in combination with fulvestrant, a single-arm, open-label Phase II portion with 60 postmenopausal patients with locally recurrent or metastatic HER2-negative, hormone receptor–positive breast cancer has been added to this study. This Phase II portion is distinct from Cohort F in that patients cannot have received prior fulvestrant and cannot have received more than one prior chemotherapy for treatment of their breast cancer.

Multiple lines of nonclinical and clinical data support a key role for the PI3K pathway in the generation of resistance to hormonal therapies. Activation of the PI3K pathway (via *PIK3CA* mutations, loss of PTEN expression, or HER2 overexpression) has been demonstrated to promote resistance to anti-estrogen therapy and hormonal independence in ER-positive breast cancer models (Shou et al. 2004;

Miller et al. 2009, 2010). Proteomic and transcriptional profiling of human hormone receptor–positive tumors suggest that increased PI3K signaling is associated with lower ER levels, which has been correlated with resistance to endocrine therapy (Creighton et al. 2010; Miller et al. 2010). Retrospective analyses of tumor samples from hormone receptor–positive patients treated with tamoxifen lend support to the nonclinical observations linking the PI3K pathway to resistance to anti-estrogen therapy; patients with an activated PI3K pathway have been found to have decreased overall survival (OS) (Kirkegaard et al. 2005) and shorter relapse-free survival (Shoman et al. 2005). Inhibition of the PI3K/mTOR pathway in nonclinical models has been shown to upregulate ER/PgR expression (Creighton et al. 2010) and enhance the anti-tumor effect of letrozole (Boulay et al. 2005).

In the clinical setting, data from two Phase II studies suggest that the combined inhibition of the PI3K/mTOR and estrogen-signaling pathway may provide superior benefit when compared with single-agent endocrine therapies. Administration of the rapamycin analog, everolimus, increased the efficacy of letrozole in the neoadjuvant setting in a Phase II study with patients with ER-positive breast cancer as measured by a decrease in Ki67 expression (Baselga et al. 2009). The addition of everolimus to tamoxifen in a Phase II study with ER-positive patients who received prior treatment with an aromatase inhibitor (AI) significantly improved the clinical benefit rate (CBR), time to progression, and overall survival compared with single-agent tamoxifen (Bachelot et al. 2012). Finally, data from the Phase III BOLERO-2 study demonstrated that the addition of everolimus to exemestane more than doubled progression-free survival (PFS) compared with single-agent exemestane in ER-positive, HER2-negative patients with metastatic breast cancer (MBC) whose disease was refractory to prior treatment with letrozole or anastrozole (Baselga et al. 2012). Therefore, the combined inhibition of the ER and PI3K-pathways may prove to be an effective therapy in patients with MBC who experience recurrent or progressive disease while receiving treatment with an AI.

1.4.3 Benefit-Risk Assessment

The anticipated or potential safety issues associated with administration of GDC-0032 as a single-agent or in combination with either letrozole or fulvestrant and the measures to be taken that are intended to avoid or minimize such toxicities in this trial are described in detail in Section 3.4.

Due to the need to develop improved anti-cancer therapies and on the basis of the clinical and nonclinical data available for GDC-0032, Genentech has assessed the risk-benefit profile of GDC-0032 as either a single-agent in patients with solid tumors or non-Hodgkin's lymphoma in combination with either letrozole or fulvestrant in patients with hormone receptor–positive advanced breast cancer to be favorable in the proposed clinical trial.

2. OBJECTIVES

2.1 PHASE I: OBJECTIVES (STAGE 1 AND STAGE 2)

2.1.1 Phase I: Primary Objectives

The primary objectives of this study are the following:

- Stage 1: To evaluate the safety and tolerability of escalating doses of GDC-0032 administered daily for 28 days to patients with locally advanced or metastatic solid tumors.
- Stage 1: To determine the MTD of GDC-0032 and to characterize dose-limiting toxicities (DLTs) associated with GDC-0032 when administered daily for 28 days to patients with locally advanced or metastatic solid tumors
- To characterize the pharmacokinetic (PK) properties of GDC-0032
- To identify a recommended dose and schedule of single-agent GDC-0032 for future trials
- To evaluate the safety and tolerability of concomitant daily administration of GDC-0032 and letrozole in postmenopausal patients with locally advanced or metastatic hormone receptor–positive breast cancer
- To evaluate the safety and tolerability of concomitant administration of GDC-0032 and fulvestrant in postmenopausal patients with locally advanced or metastatic hormone receptor–positive breast cancer
- To evaluate the safety and tolerability of GDC-0032 in patients with non-Hodgkin's lymphoma
- To evaluate the safety and tolerability of GDC-0032 in patients with *PIK3CA*-mutant locally advanced or metastatic solid tumors

2.1.2 Phase I: Secondary Objectives

The secondary objectives of this study are the following:

- To make a preliminary assessment of the anti-tumor activity of single-agent GDC-0032 in patients with locally advanced or metastatic solid tumors, non-Hodgkin's lymphoma, tumors with *PIK3CA* mutations, HER2-positive breast tumors, and tumors with increased *PIK3CA* copy number
- To evaluate the effect of food on the pharmacokinetics of GDC-0032
- To evaluate the effect of GDC-0032 on the pharmacokinetics of midazolam
- To assess the pharmacokinetics of GDC-0032 and letrozole following administration of GDC-0032 in combination with letrozole
- To assess the pharmacokinetics of GDC-0032 and fulvestrant following administration of GDC-0032 in combination with fulvestrant
- To make a preliminary assessment of the anti-tumor activity of GDC-0032 in combination with letrozole in patients with locally advanced or metastatic hormone receptor–positive breast cancer

- To make a preliminary assessment of the anti-tumor activity of GDC-0032 in combination with fulvestrant in patients with locally advanced or metastatic hormone receptor–positive breast cancer

2.1.3 Phase I: Exploratory Objectives

The exploratory objectives of this study are the following:

- To determine the proportion of *PI3K* mutations, *PI3K* amplifications, and loss of PTEN expression in archival tissue and/or in circulating tumor DNA (ctDNA) and/or circulating tumor cells (CTCs) from blood obtained from patients in this study
- To make a preliminary assessment of PD, dose, and anti-tumor activity with DNA and RNA alterations, such as, but not limited to, *PI3K*-mutation status, alterations determined by next-generation sequencing (NGS) platforms from archival and fresh tumor biopsies, DNA (ctDNA) and/or circulating tumor cells (CTCs), and patients' clinical and pathological characteristics
- To make a preliminary assessment of PD, dose, and anti-tumor activity with *PI3K*-mutation status, BCL2 and MYC expression, *BCL2* and *MYC* rearrangement, cell-of-origin subtype, and DNA and RNA alterations determined by NGS in patients with relapsed or refractory DLBCL
- To evaluate changes in tumor ^{18}fluorodeoxyglucose (FDG) uptake as assessed by positron emission tomography (PET)
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to dose and anti-tumor activity
- To explore the potential role of polymorphisms in drug metabolism enzyme and transporter genes in the PK of GDC-0032
- To explore whether inhibition of PI3K results in changes in metabolic profiles in plasma and urine
- To obtain PD data on the effects of GDC-0032 in combination with letrozole on the PI3-kinase (and other) pathways using pre- and on-treatment biopsies

2.2 PHASE II: OBJECTIVES

2.2.1 Phase II: Primary Objective

The primary objective of the Phase II portion of the study is the following:

- To assess the clinical efficacy of the combination of GDC-0032 and fulvestrant, as measured by the clinical benefit rate and objective response rate, in all patients and patients with *PIK3CA*-mutant breast cancer

2.2.2 Phase II: Secondary Objectives

The secondary objectives of the Phase II portion of this study are the following:

- To assess the clinical efficacy of GDC-0032 and fulvestrant, as measured by duration of response, PFS, and OS in all patients and patients with *PIK3CA* mutant breast cancer

- To determine the nature, severity, and frequency of adverse events associated with the combination of GDC-0032 and fulvestrant
- To evaluate plasma concentrations of GDC-0032 and fulvestrant using a sparse sampling approach.

2.2.3 Phase II: Exploratory Objectives

The exploratory objectives of the Phase II portion of this study are the following:

- To explore the exposure-response relationship for safety and efficacy with GDC-0032 and fulvestrant
- To explore predictors of response to the combination of fulvestrant and GDC-0032 based on exploratory analyses of tumor tissue, circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and cytokine and chemokine levels from blood obtained from patients in this study

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label, multicenter, Phase I/II study. The Phase I portion is divided into two stages. Phase I, Stage 1 is a dose-escalation study using a 3 + 3 design to assess the safety, tolerability, and pharmacokinetics of GDC-0032 administered QD orally (PO) as a single agent. Phase I Stage 2 includes a cohort-expansion study to assess the safety, tolerability, pharmacokinetics, and preliminary activity of GDC-0032 administered as a single agent or in combination in multiple tumor types. In addition, Phase I Stage 2 Cohorts E and F are dose-escalation cohorts to assess GDC-0032 in combination with endocrine therapy in patients with hormone receptor–positive breast cancer. Alternate intermittent dosing schedules with GDC-0032 as either a single agent or in combination with endocrine therapy will also be evaluated in Stage 2. Patients enrolled in Phase I, Stage 1 and Stage 2 Cohorts A-G will receive GDC-0032 in capsule formulation, whereas patients in Phase I, Stage 2 Cohorts H-X will receive GDC-0032 in tablet formulation. See below for detailed descriptions of the individual cohorts.

The Phase II portion is an open-label, single-arm study to assess the clinical activity of GDC-0032 in capsule formulation administered QD orally in combination with fulvestrant.

Approximately 563–663 patients will be enrolled into Phase I of this study. Stage 1 (dose escalation stage) of the Phase I portion of this study has completed enrollment with 34 patients enrolled. Stage 2 (cohort expansion stage) of Phase I will enroll approximately 529–629 patients with locally advanced or metastatic solid tumors or non-Hodgkin's lymphoma for which standard therapy either does not exist or has proven ineffective.

The Phase II portion of this study has completed enrollment with 60 postmenopausal patients with locally recurrent or metastatic hormone receptor–positive breast cancer enrolled.

All patients will be carefully followed for adverse events throughout the study (see Sections 4.5.4 for study duration), which will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0).

Patients will be enrolled at sites in the United States, Canada, and Europe.

The Sponsor has decided to discontinue enrollment in the study as of 28 June 2018 and discontinue manufacturing of GDC-0032. This decision was based on the results of the primary analysis of Study GO29058, a Phase III study of GDC-0032 in combination with fulvestrant for the treatment of metastatic, hormone receptor–positive breast cancer (GO29058), which showed that GDC-0032 plus fulvestrant had modest clinical benefit and limited overall tolerability. Patients participating in the study as of 28 June 2018 will continue to receive treatment and undergo assessments (as outlined in Appendix A-7) until 6 months after enrollment of the last patient (last patient in [LPI] +6 months). After this time, patients who are deriving clinical benefit from GDC-0032, as determined by the investigator, may continue their assigned treatment regimen until disease progression, unacceptable toxicity, expiration of the last batch of GDC-0032 (expected by May 2021), or discontinuation of the study by the Sponsor, whichever occurs first. Patients continuing treatment beyond LPI +6 months will undergo a reduced set of assessments, as outlined in Appendix A-9). Beyond LPI + 6 months, discontinuation of GDC-0032 treatment will also constitute discontinuation from the study. Survival follow-up will be halted as of LPI + 6 months.

3.1.1 Phase I

There are two stages to the Phase I portion of this study: Stage 1 (dose escalation) and Stage 2 (expansion). Each stage consists of three study periods: a screening period of 14 days or less, followed by a treatment period of up to 5 years, and a 30-day follow-up period. See Figure 1–Figure 3 for the study schemas.

Stage 1 will examine the safety and pharmacokinetics of increasing doses of GDC-0032 administered daily in a 28-day cycle in patients with locally advanced or metastatic solid tumors for which standard therapy either does not exist or has proven ineffective or intolerable. Thirty-four patients were enrolled in Stage 1, which has been completed. See Section 3.1.3 for details on Stage 1. Refer to the Taselisib (GDC-0032) Investigator's Brochure for further information.

DLTs will be assessed during the DLT assessment window (Days 1–35 of Cycle 1 in Stage 1 and Days 1–28 in Stage 2, Cohorts E and F; see Section 3.1.4 and Section 3.1.5, respectively).

Stage 2 is designed to provide a preliminary assessment of single-agent activity with GDC-0032 and in combination with endocrine therapy to better characterize the safety, tolerability, and PD and PK variability of different doses and schedules for future studies.

The pharmacokinetics and safety profile of GDC-0032 as a single-agent will be assessed in Cohorts A, B, C, D, G, H, T, T2, and X. The pharmacokinetics and safety profile of GDC-0032 in combination with letrozole will be assessed in Cohorts E, N, P, Q, R, and S. The pharmacokinetics and safety profile of GDC-0032 in combination with fulvestrant will be assessed in Cohorts F, J, K, L, and M. See Section 3.1.4 for details on Stage 2.

Pharmacokinetics (PK): GDC-0032 pharmacokinetics will be evaluated in both stages (see Sections 3.1.4 and 3.1.5 for specific PK assessments). Changes to PK sampling times, slower dose escalation, and/or changes to the dosing schedule may be implemented on the basis of the results of PK analyses. Additional PK sampling may occur if GDC-0032 is held for an adverse event in order to better characterize the safety profile of GDC-0032.

Pharmacodynamics (PD): PD analyses will include imaging studies and assessments of PD biomarkers in both tumor tissue and blood:

Blood samples for platelet-rich plasma: In Stage 1 only, blood samples will be collected at various timepoints and processed to obtain platelet-rich plasma to explore changes in surrogate PD markers in response to GDC-0032.

Circulating tumor cells (CTC) analyses: Blood samples will be collected for analyses of CTCs from all patients pretreatment, on Day 15 or Day 16 of Cycle 1, on Day 1 of Cycle 3, at the study completion visit, and also at the clinic visit subsequent to a confirmed partial or complete tumor response (per Response Evaluation Criteria in Solid Tumors [RECIST]) for any patient (see Appendices A-1 to A-7), except for patients enrolled in Cohorts Q, R, S, T, T2, and X.

Circulating tumor DNA analysis: Blood samples for DNA sequencing to identify *PIK3CA* and cancer-related mutations in ctDNA will be collected from all patients pretreatment, Cycle 3 Day 1, Cycle 5 Day 1, at the study completion visit, and also at clinic visits on Day 1 of every odd-numbered cycle subsequent to a confirmed partial or complete tumor or lymphoma response for any patient (see Appendices A-1 to A-7).

Paired tumor biopsies: Optional paired tumor biopsy samples for patients in Stages 1 and 2 will be obtained pretreatment (prior to initiation of treatment with GDC-0032 on Day 1 of Cycle 1) and on-treatment during Cycle 1, between Days 15–21 (see Section 4.5.1.n). A tumor biopsy upon progression of disease will also be optional in this trial. From each of Cohorts N and P, a minimum of 3 patients with *PIK3CA*-mutant tumors and 3 patients with *PIK3CA*-wild-type tumors (12 total) are required to provide fresh pre-treatment and on-treatment (Cycle 1 Days 15–21, 1–4 hours post-GDC-0032 dose) biopsy samples to assess the effects of GDC-0032 on the PI3K (and other) pathways in the 2-mg and 4-mg tablet doses in combination with letrozole. In Cohort X3, a minimum of 5 patients are required to provide fresh pre-treatment and on-treatment biopsy samples to assess the effects of GDC-0032 on PI3K (and other cancer-related) pathways in HNSCC. If the tissue

is not evaluable for these PD measurements, additional patients may be enrolled to complete the cohort.

FDG-PET imaging (includes FDG-PET and/or FDG-PET/CT scans) will be optional for patients in Phase I Stage 1, Cohort 1 but mandatory for patients in Stage 1, Cohorts ≥ 2 and in selected cohorts of Phase I Stage 2 (A-G, L, M, N, Q, R, and S). Patients will undergo FDG-PET imaging pretreatment (within 14 days before Cycle 1, Day 1), during the last week of Cycle 1 (e.g., between Days 29–35 [Stage 1] or Days 22–28 [Stage 2]), and at the end of Cycle 2 (between Days 22–28). If the pretreatment FDG-PET imaging for a patient shows no detectable tumor FDG uptake, then subsequent FDG-PET imaging will not be required for that patient. If there are no significant changes in FDG-PET in Cycle 1, FDG-PET imaging should not be obtained in Cycle 2 (see Section 4.5.1 and Appendices A-1–A-7). FDG-PET results will not be used for assessments of response or progression or for decisions regarding continuation of study treatment or study discontinuation, as FDG-PET has not been validated as an indicator of early response or progression in this setting.

Pharmacogenetic analysis: A blood sample for DNA isolation will be collected from all patients in this study for potential pharmacogenetic analysis of genes that may affect the pharmacokinetics of or response to GDC-0032.

Efficacy analysis: Disease status will be assessed using RECIST v1.1 (see Appendix C), except for Cohort T, which will use the Revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (see Appendix I) and Cohort T2, which will use a modified version of the Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014; see Appendix J). Patients will undergo tumor and response assessments at screening and then at the end of every even-numbered cycle (i.e., every two cycles), or earlier if clinically indicated. If a patient undergoes an interim tumor evaluation to confirm a partial response (i.e., between 4–7 weeks after previous tumor assessment), the next scheduled tumor assessment may be skipped so as to not expose patients to excessive radiation from tumor assessments.

In the absence of a DLT, unacceptable toxicity, or disease progression, patients with clinical benefit will be offered continued treatment with GDC-0032 for up to 5 years. Continued dosing beyond Cycle 1 will be at the discretion of the investigator, after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Patients who are benefiting from GDC-0032 after the 5-year treatment period may have the possibility of continued treatment, provided that study drug is available.

Patients who experience a DLT during the DLT Assessment Window (Days 1–35 of Cycle 1 for Stage 1 and Days 1–28 of Cycle 1 for Stage 2, Cohorts E and F), experience disease progression or unacceptable toxicity at any time during the study, or, in their opinion or the opinion of the investigator, are not benefiting from GDC-0032, will be discontinued from GDC-0032 study treatment. In some cases, if the

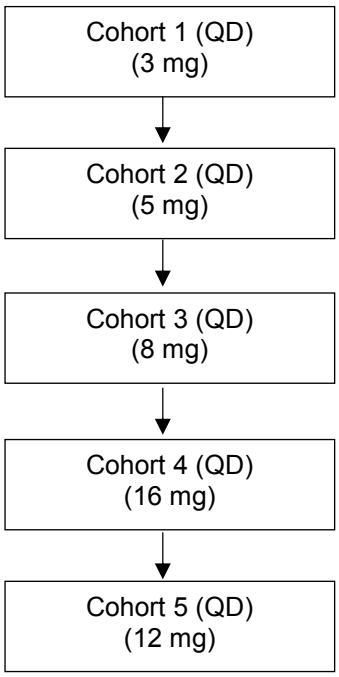
adverse event is reversible and monitorable and the risk/benefit assessment suggests a reasonable rationale for continued treatment with study drug, patients may be allowed to continue with study treatment with agreement by the investigator and the Medical Monitor. A Study Completion/Early Termination Visit will be performed approximately 30 days after the last dose of GDC-0032. The end of the study is defined as the date on which the last patient has his or her last visit (LPLV).

See Section 4.5 and Appendices A-1 to A-7, *Appendix A-9*, and B-1 to B-14 for the study assessments.

Figure 1 Phase I Study Schema (Stage 1—Dose Escalation)

Stage 1: Dose Escalation

- Enroll minimum of 3–6 patients per cohort
- Evaluate the safety, tolerability, and pharmacokinetics of GDC-0032 QD (28 days in a 28-day cycle)

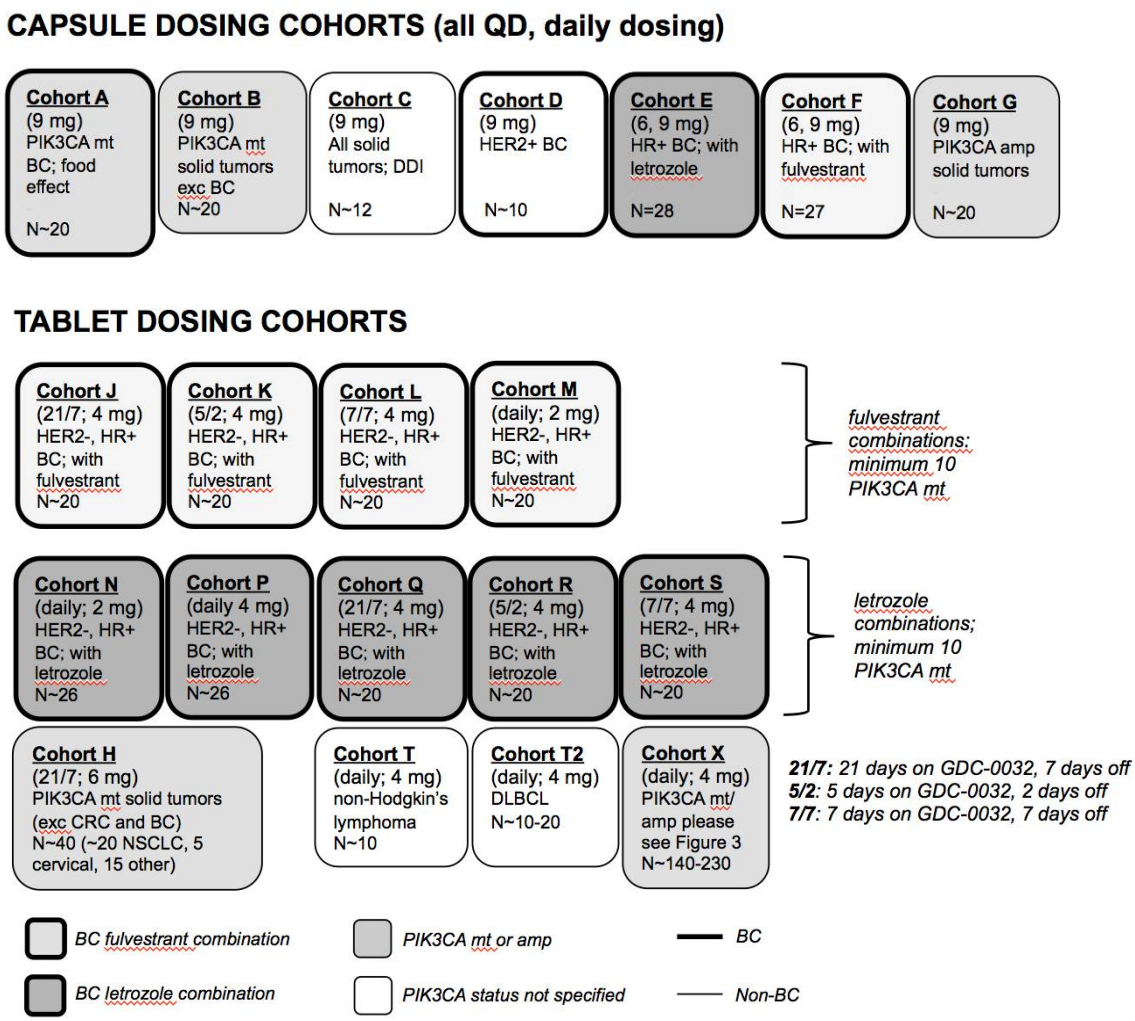


Continue dose escalation to the MTD.

Patients will undergo intensive PK sampling on Days 1 and 15 of Cycle 1.
Escalation to the next dose will be based on DLTs observed during the DLT assessment window (Days 1–35) and PK data (see Section 3.1.3).

DLT = dose-limiting toxicity (see Section 3.1.3); MTD = maximum tolerated dose; PK = pharmacokinetic; QD = once per day; TBD = to be determined.

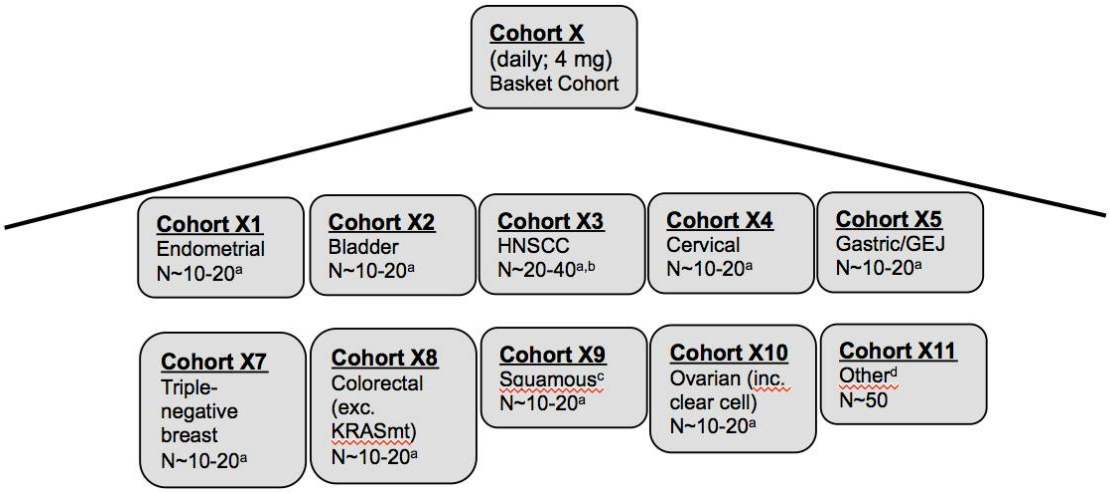
Figure 2 Phase I Study Schema (Stage 2–Expansion)



amp = amplified; BC = breast cancer; CRC = colorectal cancer; DDI = drug-drug interaction with midazolam; exc = excluding; mt = mutant; DLBCL = diffuse large B-cell lymphoma, NSCLC = non–small cell lung cancer.

Note: Amendment 9 adds Cohort T2 and decreases the dose in Cohorts T and X from 6 mg to 4 mg.

Figure 3 Phase I Study Schema (Stage 2–Cohort X)



exc = excluding; GEJ = gastroesophageal junction; HNSCC = head and neck squamous cell carcinoma; inc = including; mt = mutant.

[a] Cohorts X1–X10: If response rate ≥ 20% in the first 10 patients, an additional 10 patients will be added.

[b] Cohort X3: 10–20 patients with mutant PIK3CA HNSCC, regardless of *PIK3CA* copy number status; and 10–20 patients with HNSCC with amplification of the PIK3CA gene and no PIK3CA somatic mutations detected.

[c] Cohort X9: *PIK3CA*-mutant squamous cell cancer excluding histologies in Cohorts X1–X8 and X10 and NSCLC.

[d] Cohort X11: *PIK3CA*-mutant solid tumors not otherwise specified in Cohorts X1–X10 and excluding breast, NSCLC, and colorectal cancer. Small cell lung cancer is allowed in Cohort X11.

Note: Amendment 9 eliminates Cohort X6 and changes the Cohort X starting dose of GDC-0032 from 6 mg to 4 mg.

3.1.2 Phase II

The Phase II portion of this study is designed to provide safety and efficacy data on the combination of fulvestrant and GDC-0032. Based on the Phase I (Stage 1 and Stage 2) clinical data, the recommended Phase II dose of GDC-0032 in combination with fulvestrant has been determined to be 6 mg QD.

In the Phase II portion of the study, approximately 60 postmenopausal patients with locally advanced or metastatic HER2-negative, hormone receptor–positive breast cancer who have not previously received fulvestrant will be enrolled in this study at sites in the United States and in Europe. A minimum of 30 patients will have *PIK3CA*-mutant breast cancer (see Figure 4).

All patients will be carefully followed for adverse events throughout the study, which will be graded according to NCI CTCAE v4.0.

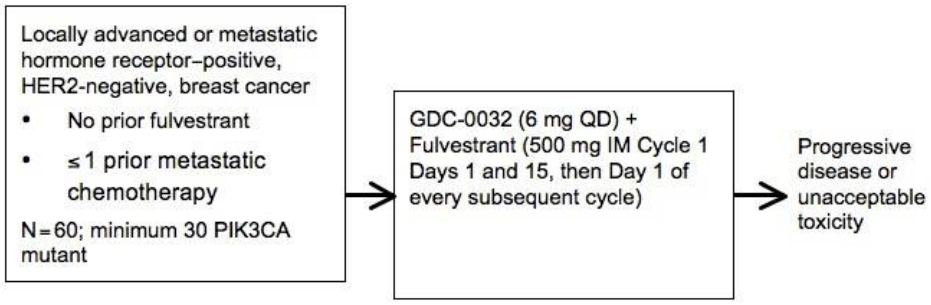
GDC-0032 and fulvestrant plasma concentrations will be evaluated using a sparse sampling approach (see Appendices A-8 and B-9). Additional PK sampling may occur if GDC-0032 is held for an adverse event in order to better characterize the safety profile of GDC-0032.

PD analyses will include assessments of PD biomarkers in both tumor tissue and blood. Blood samples will be collected for analyses of CTCs, ctDNA, and cytokines and chemokines as described in Appendix A-8. Paired tumor biopsy samples obtained pretreatment (prior to initiation of treatment with GDC-0032 on Day 1 of Cycle 1) and during Cycle 2 will be optional for patients. A tumor biopsy upon progression of disease will also be optional.

Disease status will be assessed using RECIST v1.1 (see Appendix C). Patients will undergo tumor and response assessments at screening and then at timepoints as described in Appendix A-8, or earlier if clinically indicated. Bone scans will be performed as described in Appendix A-8.

All patients who discontinue from the treatment phase will be followed for survival information and subsequent anti-cancer therapies unless the patient requests to be withdrawn from study survival follow-up. Survival follow-up information will be collected via telephone calls, patient's medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by Genentech.

Figure 4 Phase II Study Schema



IM = intramuscular; QD = once per day.

3.1.3 Stage 1: Dose Escalation to Estimate the Maximum Tolerated Dose

Approximately 24–42 evaluable patients (3–6 per dose-level cohort) will be enrolled in Stage 1. The starting GDC-0032 dose will be 3 mg QD PO. The number of patients and cohorts may increase if additional cohorts are enrolled.

In Stage 1, Cycle 1 will be 35 days in length and will begin with a PK evaluation, during which all patients will receive a single fasting dose of GDC-0032 on Day 1 at their assigned dose level. The initial dose will be followed by a 7-day washout and frequent PK sampling up to 72 hours to determine the single-dose PK properties of GDC-0032 in humans. Urine samples will be collected up to 24 hours after the first dose to determine urinary elimination of GDC-0032. Blood samples will be taken at several scheduled timepoints to explore the surrogate PD response after a single dose. Continuous daily dosing will begin on Day 8 and will continue for 4 weeks (Days 8–35). Subsequent cycles will be 28 days in length (4 weeks of daily dosing).

DLTs will be assessed during the DLT assessment window (Days 1–35 of Cycle 1 in Stage 1).

In Stage 1, steady-state pharmacokinetics of GDC-0032 will be evaluated following the dose on Day 15. Additional blood samples will be taken prior to dosing on Days 8, 16, 22, and 29 during Cycle 1 and at the start of each subsequent cycle (Cycles ≥ 2) to monitor the exposures of GDC-0032 after continuous daily dosing (see Appendix B-1). Changes to PK sampling times, slower dose escalation, and/or changes to the dosing schedule may be implemented on the basis of the results of PK analyses.

Patients will be evaluable for DLT starting after the receipt of a single dose of GDC-0032. Patients who withdraw or are withdrawn from the study prior to completing the DLT assessment window for any reason other than a DLT will be replaced. In addition, patients who miss four or more total doses of GDC-0032 during the DLT assessment window for reasons other than a DLT will be replaced by another in that cohort. Patients will not be allowed to make up missed doses at a later time; patients will resume dosing at their next scheduled dose. Continuation of study treatment may occur after an assessment of compliance and discussion between the investigator and the Medical Monitor.

Dose escalation will continue in accordance with the dose-escalation rules described in Section 3.1.3.b until the MTD is exceeded, excessive pill burden is declared, or analysis of available PK data indicates that exposure will not increase with further increases in the dose of GDC-0032.

a. Definition of Dose-Limiting Toxicity

All adverse events will be reported, with severity assessed according to the NCI CTCAE v4.0. For dose escalation purposes, DLT assessments will be reviewed by the Sponsor. A DLT is defined as any one of the following toxicities occurring within the DLT Assessment Window (Cycle 1, Days 1–35) assessed by the investigator to be possibly related to GDC-0032 per Section 5.2 or Section 5.3:

- Grade ≥ 3 non-hematologic, non-hepatic organ system, non-metabolic (hyperglycemia and hyperlipidemia) toxicity, excluding the following:
- Alopecia of any grade

- Grade 3 diarrhea that responds to standard-of-care therapy
- Grade 3 nausea or vomiting, in the absence of premedication, that responds to standard-of-care therapy
- Grade ≥ 4 thrombocytopenia
- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] $< 500/\mu L$) lasting > 5 days or accompanied by fever (oral or tympanic temperature $\geq 38.0°C$)
- Fasting Grade ≥ 4 hyperglycemia
- Fasting Grade ≥ 3 hyperglycemia for ≥ 1 week, despite adequate trial of oral anti-hyperglycemic therapy
- Grade ≥ 4 fasting hypercholesterolemia or triglyceridemia for ≥ 2 weeks despite intervention with a lipid-lowering agent
- Grade ≥ 3 serum bilirubin or hepatic transaminase (ALT or AST)
- For patients with Grade 1 hepatic transaminase at baseline as a result of liver or bone metastases, hepatic transaminase $\geq 7.5\times$ the upper limit of normal (ULN) will be considered a DLT.
- For patients with liver metastases, total bilirubin $\geq 5\times$ the ULN will be considered a DLT, or $10\times$ the ULN with Gilbert's disease and with Grade 2 bilirubin at baseline.
- For patients with Grade 2 alkaline phosphatase at baseline as a result of bone metastasis or alkaline phosphatase-secreting osteosarcoma, an alkaline phosphatase at ≥ 10 times the ULN will be considered a DLT.

b. Dose-Escalation Rules

Dose escalation will occur in Stage 1. Enrollment of the first 2 patients in the first cohort will be staggered by approximately 1 week. Dose escalation will occur in accordance with the following rules:

- A minimum of 3 patients will be initially enrolled per cohort. If none of these patients experiences a DLT, escalation will proceed to the next higher dose level. If 1 of these patients experiences a DLT, the cohort will be expanded to at least 6 patients.
- If ≥ 2 patients in a given cohort experience a DLT during the DLT assessment window, the MTD (defined as the highest dose level at which $< 33\%$ of patients develop a DLT during the DLT assessment window) will have been exceeded and dose escalation will stop; 3 additional patients will be evaluated for DLT at the preceding dose level, if 6 patients had not already been dosed at that level.
- If the dose level at which the MTD is exceeded or excessive pill burden is encountered is $> 35\%$ of the previous dose level, a subsequent dose level may be evaluated and will be an average of the two highest dose levels. For example, if the MTD is exceeded at 1000 mg and the previous dose level was 600 mg (a 67% increase), the next dose level would be $(600 + 1000)/2 = 800$ mg.

After the first cohort, dose levels will increase by 100% until a safety signal is observed (DLT or if ≥ 2 patients experience a Grade 2 GDC-0032–related adverse event, excluding transaminase elevations, anemia, and neutropenia). Thereafter, dose levels

will increase by 50% or less until a second safety signal is observed (DLT or if ≥2 patients experience a Grade 2 GDC-0032-related adverse event, excluding transaminase elevations, anemia, and neutropenia). There will then be a single dose escalation of 40%. All subsequent dose escalations will be 33%. The actual dose may be rounded up or down based on availability of different capsule strengths. On the basis of the review of real-time safety and available preliminary PK data from this study with GDC-0032, dose escalation may be halted or modified by Genentech as deemed appropriate.

The decision for dose escalation will be made by a committee composed of the following Sponsor representatives: the Medical Monitor, clinical scientist, statistician, and safety scientist, in consultation with the PK scientist and clinical trial manager. This committee will review available data on demographics, safety and adverse events, laboratory assessments, ECGs, dose administration, pharmacokinetics, and imaging studies. Based on a review of these data and in consultation with the participating investigators, a determination will be made as to whether dose escalation should continue and, if so, at what dose level.

3.1.4 Stage 2: Expanded Cohorts in Specific Disease or Patient Subsets

Approximately 529-629 patients will be enrolled across 19 cohorts in Phase I, Stage 2 to better characterize the safety profile, PK parameters, and preliminary activity of GDC-0032 at different doses and schedules in specific disease or patient subsets as a single agent (Cohorts, A, B, C, D, G, H, T, T2, and X), in combination with letrozole (Cohorts E, N, P, Q, R, and S), and in combination with fulvestrant (Cohorts F, J, K, L, and M). All patients enrolled in Cohorts H-X will receive GDC-0032 in tablet form at doses of 2, 4, or 6 mg (equivalent to capsules at 3, 6, and 9 mg, respectively).

Additional patients may be enrolled to achieve a sufficient number of patients who are evaluable for safety and PK in each cohort as specified below, if some patients do not have sufficient safety and PK data for analysis (see Section 4.9.10 for justification of the sample size for the expansion cohorts). The decision as to whether to enroll fewer than 529 patients in Stage 2 will be made by the Sponsor, based on available safety and efficacy data and the rate of enrollment in a particular cohort. To facilitate optimal operation of this complex trial, and taking into account safety and efficacy data, certain cohorts may be opened and enrolled in a staggered fashion (e.g., Cohort J before Cohort L). This is especially applicable for expansion cohorts with similar inclusion and exclusion criteria (Cohorts J–M and N–S).

The Stage 2 dose for single-agent GDC-0032 (Cohorts A–D, G, H, T, and X) is the recommended dose for future studies according to criteria specified in Section 3.2.5 and will depend on the overall safety and tolerability while maximizing anticipated biological effect on PI3K inhibition. All patients enrolled in Cohorts A–G will receive GDC-0032 in capsule form. All patients enrolled in Cohorts H-X will receive GDC-0032 in tablet form

at doses of 2, 4, or 6 mg (equivalent to capsules at 3, 6, and 9 mg, respectively). The GDC-0032 dose in combination with endocrine therapy in Stage 2 (Cohorts E and F) will be established using the dose escalation rules described in Sections 3.1.4.e and 3.1.4.f. Additionally, safety, tolerability, and preliminary efficacy data from Cohorts J–N and P–S will aim to evaluate additional doses and alternative dosing schedules and thus help with a robust risk assessment with each of the endocrine therapy combinations. Dose levels and schedules for various cohorts are described below.

In Stage 2, Cycle 1 will be 28–35 days in length, depending on the specific cohort. Subsequent cycles will be 28 days in length (4 weeks of daily dosing). See Figure 5 for the Stage 2 dosing and PK sample collection.

If the frequency of Grade 3 or 4 toxicities or other unacceptable chronic toxicities in Stage 2 suggests that the MTD has been exceeded at that dose level, any remaining accrual at that dose level will be halted. Consideration will then be given to enrolling an expansion cohort at the next lower dose level (as defined in Section 4.3.3 and Table 5), up to the specified number of patients (as described in Section 3.1).

Capsule Dosing Cohorts (Cohorts A-G):

a. Cohort A

Approximately 20 patients with *PIK3CA*-mutant breast cancer will be enrolled in Cohort A. The initial dose of GDC-0032 will be given on Day 1, followed by a 7-day washout period. Continuous daily dosing in Cycle 1 of GDC-0032 will begin on Day 8 and will continue for 4 weeks (Days 8–35). See Appendix A-2 for the schedule of assessments and Appendix B-2 for the schedule of PK sample collection.

GDC-0032 appears to be a Biopharmaceutics Classification System (BCS) Class II compound (see Section 3.2.4). Since food impacts the pharmacokinetics of some BCS Class II compounds, the effect of food on the pharmacokinetics of GDC-0032 will be assessed in Cohort A.

A single standard high-fat meal (according to the U.S. Food and Drug Administration [FDA] guidelines) will be given to patients on either Day 1 or Day 8 of Cycle 1, followed by their daily dose of GDC-0032 (see Section 3.2.4). Patients will be assigned in an alternating fashion to either Day 1 (odd-numbered patients) or Day 8 (even-numbered patients) for the food-effect assessment. PK profiles up to 24 hours after dosing on Days 1 and 8 will be compared to assess food effect (see Section 3.2.4). Selection of the single-agent dose and schedule for future studies will be based on a safe and tolerable dose and schedule that achieves a reasonable exposure and PD effect.

b. Cohort B

Approximately 20 patients with *PIK3CA*-mutant solid tumors other than breast cancer will be enrolled in Cohort B. GDC-0032 will be administered daily beginning on Day 1 of

Cycle 1 and will continue for 4 weeks (Days 1–28). See Appendix A-3 for the schedule of assessments and Appendix B-3 for the schedule of PK sample collection.

c. Cohort C

Approximately 13 patients with solid tumor (any type) will be enrolled in Cohort C to assess the safety profile and the pharmacokinetic interactions of midazolam, a CYP3A4 substrate, and GDC-0032. Midazolam will be administered on Days 1 and 16 of Cycle 1. Daily oral administration of GDC-0032 will start on Day 2 and will continue for 4 weeks (Days 2–29). Additional patients may be enrolled to obtain a complete data set from 12 patients who are evaluable for PK analysis. See Appendix A-4 for the schedule of assessments and Appendix B-4 for schedule of PK sample collection.

d. Cohort D

Approximately 10 patients with HER2-positive breast cancer will be enrolled in this cohort to assess the safety profile, pharmacokinetics, and treatment effect of GDC-0032 in this patient population. GDC-0032 will be administered daily beginning on Day 1 of Cycle 1 and will continue for 4 weeks (Days 1-28). See Appendix A-3 for the schedule of assessments and Appendix B-3 for the schedule of PK sample collection.

e. Cohort E

Approximately 28 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 in combination with letrozole in this patient population. A minimum of 10 of these patients enrolled at the recommended GDC-0032 Phase II dose in combination with letrozole will be required to have *PIK3CA*-mutant breast cancer. Patients enrolled in Cohort E will receive a GDC-0032 dose level in combination with letrozole (see Section 3.2.5) that will be at or below the recommended single-agent dose and schedule. The initial dose level of GDC-0032 in Cohort E will be 6-mg capsule daily. If the 6 mg dose appears to be tolerated, consideration will be given to escalating the dose to 9-mg capsule daily, the recommended single-agent dose. No further dose escalation will occur above the recommended single-agent dose.

Definition of Dose-Limiting Toxicity

GDC-0032 and letrozole in Cycle 1 will be administered daily beginning on Day 1 and will continue for 4 weeks (Days 1-28). DLTs will be assessed during the DLT assessment window (Days 1-28 of Cycle 1) using the DLT definitions in Section 3.1.3.a.

Patients will be evaluable for a DLT starting after the receipt of a single dose of GDC-0032. Patients who withdraw or are withdrawn from the study prior to completing the DLT assessment window for any reason other than a DLT will be replaced. In addition, patients who miss four or more total doses of GDC-0032 during the DLT assessment window for reasons other than a DLT will be replaced by another patient in that cohort. Patients in Cohort E who miss four or more total doses of letrozole during

the DLT assessment window for reasons other than a DLT will be replaced by another patient in that cohort. Letrozole doses do not necessarily need to be held for GDC-0032-related adverse events. Patients will not be allowed to make up missed doses at a later time; patients will resume dosing at their next scheduled dose. Continuation of study treatment may occur after an assessment of compliance and discussion between the investigator and the Medical Monitor.

Determination of the Recommended GDC-0032 Dose in Combination with Letrozole for Future Studies

Dose escalation will occur in accordance with the following rules:

- A minimum of 3 patients will be initially enrolled per cohort. If none of these patients experiences a DLT, escalation may proceed to the next higher dose level. If 1 of these patients experiences a DLT, the cohort will be expanded to at least 6 patients.
- If ≥ 2 patients in a given cohort experience a DLT during the DLT assessment window, the MTD (defined as the highest dose level at which $< 33\%$ of patients develop a DLT during the DLT assessment window) will have been exceeded and dose escalation will stop; 3 additional patients will be evaluated for DLT at the preceding dose level, if 6 patients have not already been dosed at that level.

If patients in the cohort receiving 6-mg daily GDC-0032 capsule in combination with letrozole do not exceed the MTD, then the 9-mg capsule daily dose level in combination with letrozole may be tested.

If patients in the cohort receiving 6-mg daily GDC-0032 capsule in combination with letrozole exceeds the MTD, then a 3-mg daily GDC-0032 capsule dose level in combination with letrozole may be tested.

On the basis of the review of real-time safety and available preliminary PK data from this study with GDC-0032 and letrozole, dosing may be halted or modified by Genentech as deemed appropriate.

The decision for dose escalation or de-escalation will be made by a committee composed of the following Sponsor representatives: the Medical Monitor, clinical scientist, statistician, and safety scientist, in consultation with the PK scientist and clinical trial manager. This committee will review available data on demographics, safety and adverse events, laboratory assessments, ECGs, dose administration, pharmacokinetics, and imaging studies. Based on a review of these data and in consultation with the participating investigators, a determination will be made as to whether dose escalation or de-escalation should continue and, if so, at what dose level.

The selection of the recommended GDC-0032 dose in combination with letrozole for future studies will be based on safety, tolerability, PK data, and consideration of other factors pertaining to the patient population treated with letrozole. These factors include

expected duration of therapy, the overall tolerability in patients who may have a prolonged time to progression, and clinical benefit of the combination of letrozole and GDC-0032.

Schedule of Assessments and Pharmacokinetic Sample Collection

See Appendix A-5 for the schedule of assessments and Appendix B-5 for schedule of PK sample collection.

Enrollment at the Recommended GDC-0032 Dose in Combination with Letrozole for Future Studies

To establish a robust and tolerable dose of GDC-0032 in combination with letrozole, approximately 20 patients will be enrolled into Cohort E at the recommended GDC-0032 dose in combination with letrozole for future studies (e.g., 6-mg capsule dose level). More than one dose may be evaluated if it appears that there may be differences in the adverse event profile to select a dose for future studies. To evaluate less common but potentially important side effects such as pneumonitis, which is a class effect for these molecules, an enrollment of 20 patients should allow a better estimate of frequency, should this be observed (see Section 4.9.10).

f. Cohort F

Approximately 27 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 in combination with fulvestrant in this patient population. A minimum of 10 of these patients enrolled at the recommended GDC-0032 Phase II dose in combination with fulvestrant will be required to have *PIK3CA*-mutant breast cancer. The initial dose level of GDC-0032 in Cohort F will be 6-mg capsule daily. If the 6-mg dose appears to be tolerated, consideration will be given to escalating the dose to 9-mg capsule daily, the recommended single-agent dose. No further dose escalation will occur above the recommended single-agent dose.

Definition of Dose-Limiting Toxicity

GDC-0032 and fulvestrant in Cycle 1 will be administered daily beginning on Day 1 and will continue for 4 weeks (Days 1-28). DLTs will be assessed during the DLT assessment window (Days 1-28 of Cycle 1), using the DLT definitions in Section 3.1.3.a.

Patients will be evaluable for DLT starting after the receipt of a single dose of GDC-0032. Patients who withdraw or are withdrawn from the study prior to completing the DLT assessment window for any reason other than a DLT will be replaced. In addition, patients who miss four or more total doses of GDC-0032 during the DLT assessment window for reasons other than a DLT will be replaced by another patient in that cohort. Patients will not be allowed to make up missed doses at a later time; patients will resume dosing at their next scheduled dose. Patients who miss a fulvestrant dose

during the DLT assessment window for reasons other than a DLT will be replaced by another in that cohort. Fulvestrant doses do not necessarily need to be held for GDC-0032-related adverse events. Continuation of study treatment may occur after an assessment of compliance and discussion between the investigator and the Medical Monitor.

Determination of the Recommended GDC-0032 Dose in Combination with Fulvestrant for Future Studies

Dose escalation will occur in accordance with the following rules:

- A minimum of 3 patients will be initially enrolled per cohort. If none of these patients experiences a DLT, escalation may proceed to the next higher dose level. If 1 of these patients experiences a DLT, the cohort will be expanded to at least 6 patients.
- If ≥ 2 patients in a given cohort experience a DLT during the DLT assessment window, the MTD (defined as the highest dose level at which $< 33\%$ of patients develop a DLT during the DLT assessment window) will have been exceeded and dose escalation will stop; 3 additional patients will be evaluated for DLT at the preceding dose level, if 6 patients have not already been dosed at that level.

If patients in the cohort receiving 6-mg daily GDC-0032 capsule in combination with fulvestrant do not exceed the MTD, then the 9-mg capsule daily dose level in combination with fulvestrant may be tested.

If patients in the cohort receiving 6-mg daily GDC-0032 capsule in combination with fulvestrant exceeds the MTD, then a 3-mg daily GDC-0032 capsule dose level in combination with fulvestrant may be tested.

On the basis of the review of real-time safety and available preliminary PK data from this study with GDC-0032 and fulvestrant, dosing may be halted or modified by Genentech as deemed appropriate.

The decision for dose escalation or de-escalation will be made by a committee composed of the following Sponsor representatives: the Medical Monitor, clinical scientist, statistician, and safety scientist, in consultation with the PK scientist and clinical trial manager. This committee will review available data on demographics, safety and adverse events, laboratory assessments, ECGs, dose administration, pharmacokinetics, and imaging studies. Based on a review of these data and in consultation with the participating investigators, a determination will be made as to whether dose escalation or de-escalation should continue and, if so, at what dose level.

The selection of the recommended GDC-0032 dose in combination with fulvestrant for future studies will be based on safety, tolerability, PK data, and consideration of other factors pertaining to the patient population treated with fulvestrant. These factors include expected duration of therapy, the overall tolerability in patients who may have a

prolonged time to progression, and clinical benefit of the combination of fulvestrant and GDC-0032.

Schedule of Assessments and Pharmacokinetic Sample Collection

See Appendix A-5 for the schedule of assessments and Appendix B-6 for the schedule of PK sample collection.

Enrollment at the Recommended GDC-0032 Dose in Combination with Fulvestrant for Future Studies

To establish a robust and tolerable dose of GDC-0032 in combination with fulvestrant approximately 20 patients may be enrolled at the recommended GDC-0032 dose in combination with fulvestrant for future studies. More than one dose may be evaluated if it appears that there may be differences in the adverse event profile to select a dose for future studies (e.g., 6-mg capsule dose level). To evaluate less common but potentially important side effects such as pneumonitis, which is a class effect for these molecules, an enrollment of 20 patients should allow a better estimate of frequency, should this be observed (see Section 4.9.10).

g. Cohort G

Approximately 20 patients with solid tumors with increased *PIK3CA* copy number will be enrolled in this cohort to assess the safety profile, pharmacokinetics, and treatment effect of GDC-0032 in this patient population. GDC-0032 will be administered daily beginning on Day 1 of Cycle 1 and will continue for 4 weeks (Days 1–28). See Appendix A-3 for the schedule of assessments and Appendix B-3 for the schedule of PK sample collection.

Tablet Dosing Cohorts (Cohorts H-X):

h. Cohort H

Approximately 40 patients with *PIK3CA*-mutant solid tumors that are non–breast and non–colorectal cancer will be enrolled in Cohort H. GDC-0032 tablets at the 6-mg dose level will be administered daily on a 21-day on, 7-day off (21/7) schedule.
See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-7 for the schedule of PK sample collection. Cohort H must include a minimum 5 patients with cervical cancer and a minimum of 20 patients with NSCLC.

i. Cohort J

Approximately 20 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 in combination with fulvestrant in this patient population. This cohort will evaluate an alternative schedule of GDC-0032 tablets administered daily on a 21-day on, 7-day off (21/7) schedule at the 4-mg QD dose level. A minimum of 10 of these patients enrolled will be required to have *PIK3CA*-mutant breast cancer. See Appendix A-7 *and*

Appendix A-9 for the schedule of assessments and Appendix B-8 for the schedule of PK sample collection.

j. Cohort K

Approximately 20 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 in combination with fulvestrant in this patient population. This cohort will evaluate an alternative schedule of GDC-0032 tablets administered daily on a 5-day on, 2-day off (5/2) schedule at the 4-mg dose level. A minimum of 10 of these patients enrolled will be required to have *PIK3CA*-mutant breast cancer. See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-8 for the schedule of PK sample collection.

k. Cohort L

Approximately 20 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 in combination with fulvestrant in this patient population. This cohort will evaluate an alternative schedule of GDC-0032 tablets administered daily on a 7-day on, 7-day off (7/7) schedule at the 4-mg dose level. A minimum of 10 of these patients enrolled will be required to have *PIK3CA*-mutant breast cancer. See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-11 for the schedule of PK sample collection.

l. Cohort M

Approximately 20 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 in combination with fulvestrant in this patient population. This cohort will evaluate a schedule of GDC-0032 tablets administered daily in each 28-day cycle at the 2-mg dose level. A minimum of 10 of these patients enrolled will be required to have *PIK3CA*-mutant breast cancer. See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-8 for the schedule of PK sample collection.

m. Cohort N

Approximately 26 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 tablets in combination with letrozole in this patient population. This cohort will evaluate a schedule of GDC-0032 administered daily at the 2-mg QD tablet dose level. A minimum of 10 of these patients enrolled will be required to have *PIK3CA*-mutant breast cancer. A minimum of 6 of these patients (3 patients with *PIK3CA*-wild-type and 3 patients with *PIK3CA*-mutant tumors) will be required to undergo paired pre-treatment and on-treatment (Cycle 1 Days 15–21, 1–4 hours post-GDC-0032 dose) tumor biopsy samples. If the paired tumor biopsy samples are not evaluable, additional patients may be enrolled to complete the cohort.

See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-9 for the schedule of PK sample collection.

n. Cohort P

Approximately 26 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 tablets in combination with letrozole in this patient population. This cohort will evaluate GDC-0032 administered daily at the 4-mg QD tablet dose level. A minimum of 10 of these patients enrolled will be required to have *PIK3CA*-mutant breast cancer. A minimum of 6 of these patients (3 patients with *PIK3CA*-wild-type and 3 patients with *PIK3CA*-mutant tumors) will be required to undergo paired pre-treatment and on-treatment (Cycle 1 Days 15–21, 1–4 hours post-GDC-0032 dose) tumor biopsy samples. If the paired tumor biopsy samples are not evaluable, additional patients may be enrolled to complete the cohort. See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-9 for the schedule of PK sample collection.

o. Cohort Q

Approximately 20 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 tablets in combination with letrozole in this patient population. This cohort will evaluate GDC-0032 administered on a 21-day-on, 7-day-off (21/7) schedule at the 4-mg tablet dose level. A minimum of 10 of these patients enrolled will be required to have *PIK3CA*-mutant breast cancer. See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-9 for the schedule of PK sample collection.

p. Cohort R

Approximately 20 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 tablets in combination with letrozole in this patient population. This cohort will evaluate GDC-0032 administered on a 5-day-on, 2-day-off (5/2) schedule at the 4-mg tablet dose level. A minimum of 10 of these patients enrolled will be required to have *PIK3CA*-mutant breast cancer. See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-9 for the schedule of PK sample collection.

q. Cohort S

Approximately 20 postmenopausal patients with hormone receptor–positive breast cancer will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 tablets in combination with letrozole in this patient population. This cohort will evaluate GDC-0032 administered on a 7-day-on, 7-day-off (7/7) schedule at the 4-mg tablet dose level. A minimum of 10 of these patients enrolled will be required to have *PIK3CA*-mutant breast cancer. See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-12 for the schedule of PK sample collection.

r. Cohort T

Approximately 10 patients with non-Hodgkin's lymphoma that has progressed or has failed to respond to at least one prior regimen will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 in this patient population. This cohort will evaluate GDC-0032 administered daily at the 6-mg tablet dose level. In Amendment 9, the starting dose of GDC-0032 is changed to 4-mg tablet (see Section 3.2.31). There is no minimum number of patients who are required to have the *PIK3CA* mutation. See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-7 for the schedule of PK sample collection.

s. Cohort T2

Approximately 10–20 patients with DLBCL who have progressed or have failed to respond to at least one prior regimen will be enrolled to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 in this patient population. This cohort will evaluate GDC-0032 administered daily at the 4-mg tablet dose level. There is no minimum number of patients who are required to have the *PIK3CA* mutation. Patients must have available a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of DLBCL and for exploratory research on candidate biomarkers. See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-7 for the schedule of PK sample collection.

t. Cohort X (Basket Cohort)

Approximately 150–230 patients with *PIK3CA*-mutant solid tumors that have progressed or failed to respond to at least one prior regimen will be enrolled to characterize the safety, tolerability, pharmacokinetics, and efficacy of GDC-0032 in this patient population. This cohort will evaluate GDC-0032 administered daily at the 6-mg tablet dose level. In Amendment 9, the starting dose of GDC-0032 is changed to 4-mg tablet (see Section 3.2.33). For sub-Cohort X3 patients with HNSCC who have gastrostomy tubes, GDC-0032 will be administered as an extemporaneous suspension prepared at home only at sites where administration of the extemporaneous suspension is approved by the Institutional Review Board/Ethics Committee (IRB/EC).

This cohort comprises 10 different tumor types (sub-Cohorts X1 through X10) and another sub-Cohort, X11, to enroll patients with *PIK3CA*-mutant cancers not otherwise captured in the other cohorts, as shown in Figure 3. Each sub-cohort will enroll approximately 10–20 patients (sub-Cohort X11 will enroll approximately 50 patients) on the basis of initial response rates and central laboratory confirmation of *PIK3CA*-mutation status. See Section 4.9.10.b for sample size determination. As it is expected that enrollment into individual sub-cohorts may be halted independent of one another because of low enrollment or lack of responses, the total number of patients in Cohort X will be capped at approximately 230. In Amendment 9, Cohort X6 (SCLC) was removed*; any such* patients will be allowed to enroll in Cohort X11. During Amendment 9, Cohort X3 was expanded to include an additional 10–20 patients with HNSCC with

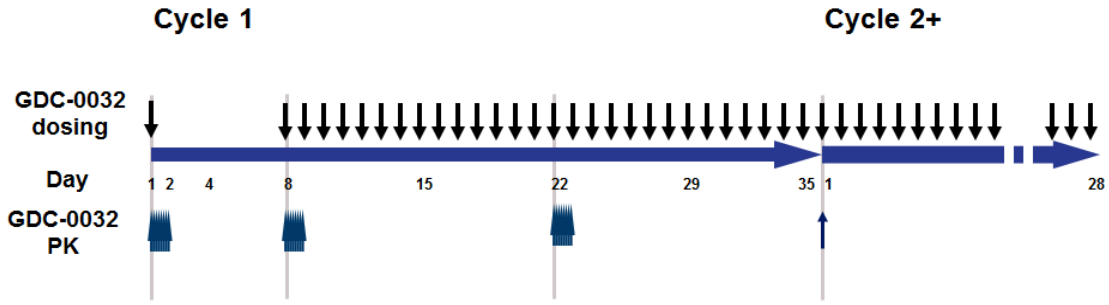
amplification of the *PIK3CA* gene and no detectable *PIK3CA* somatic mutations. The total number of patients in Cohort X3 is now 20–40.

Tumor tissue can be initially assessed for *PIK3CA* mutation or amplification status at a local or central laboratory. If locally assessed, refer to laboratory manual for definition of PIK3CA amplification. Tumor tissue must be submitted for evaluation of adequate tumor tissue content by a central laboratory, which must occur prior to initiation of study treatment. A minimum of 10 slides, preferably 15–20, should be submitted and be of good quality based on total and viable tumor content (as defined in the Laboratory Manual). If patients are enrolled in the study on the basis of a local positive test result and a mutation or amplification is not detected per central testing, additional patients may be enrolled.

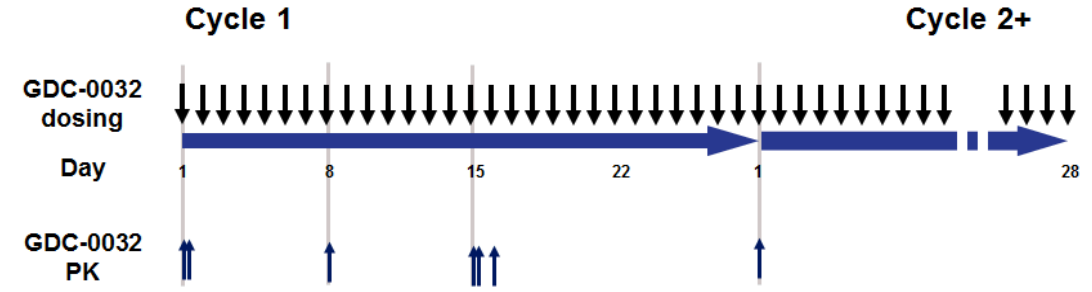
See Appendix A-7 *and Appendix A-9* for the schedule of assessments and Appendix B-7 and B-14 for the schedule of PK sample collection.

Figure 5 Phase I Stage 2 Dosing and Pharmacokinetic Sample Collection

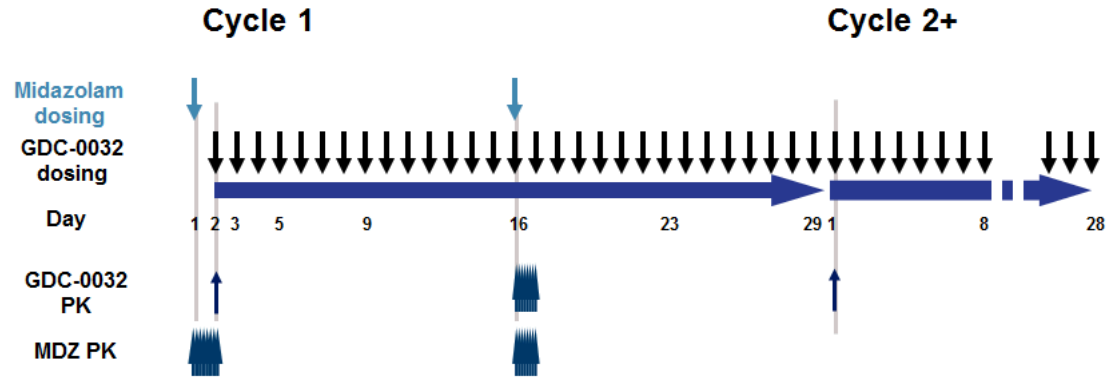
Cohort A: *PIK3CA*-Mutant Breast Cancer (Food-Effect Assessment)



Cohort B (*PIK3CA*-Mutant Solid Tumors), **Cohort D** (HER2-Positive Breast Cancer), and **Cohort G** (Solid Tumors with Increased *PIK3CA* Copy Number)



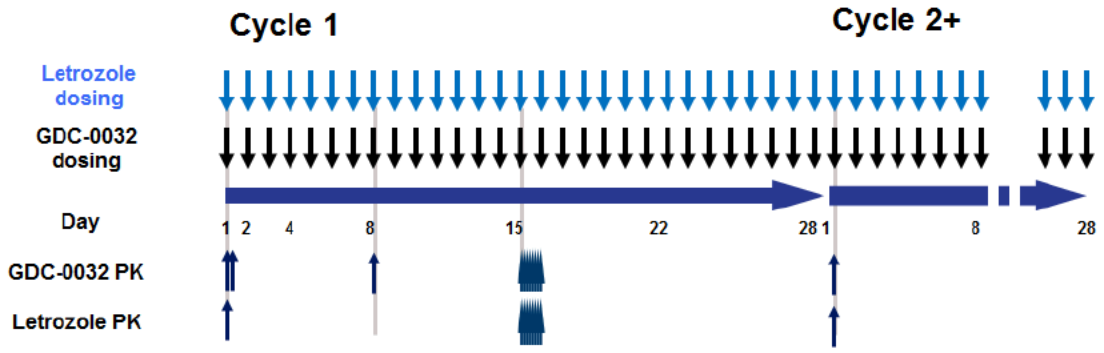
Cohort C: Solid Tumors (Midazolam Drug-Drug Interaction Assessment)



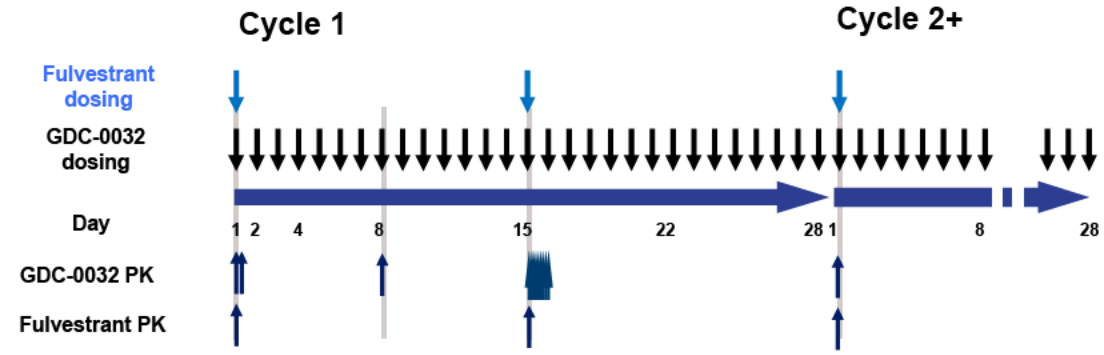
MDZ = midazolam

Figure 5 Phase I Stage 2 Dosing and Pharmacokinetic Sample Collection (cont.)

Cohort E: Hormone Receptor–Positive Breast Cancer (6-mg GDC-0032 Capsule Daily in Combination with Letrozole):



Cohort F: Hormone Receptor–Positive Breast Cancer (6 mg-GDC-0032 Capsule Daily in Combination with Fulvestrant):



Cohort H: *PIK3CA*-Mutant Solid Tumors (6-mg GDC-0032 Tablet on a 21-Day on, 7-Day off [21/7] Schedule):

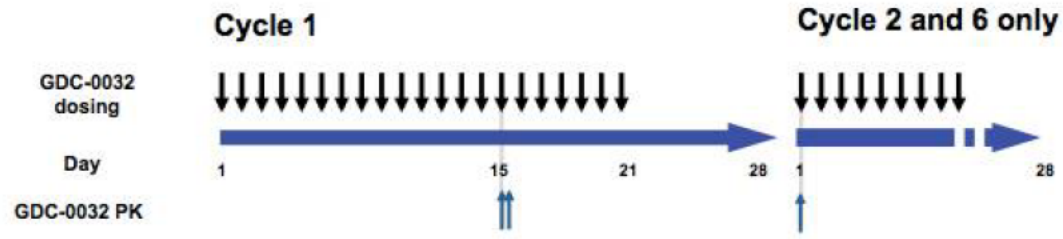
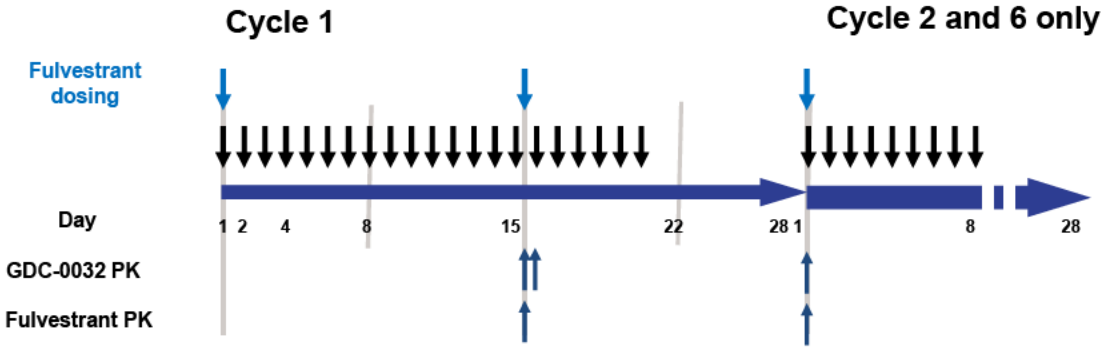
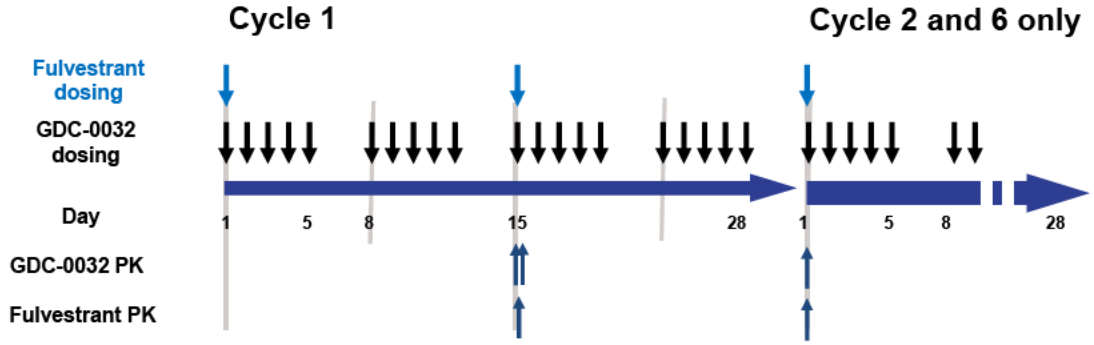


Figure 5 Phase I Stage 2 Dosing and Pharmacokinetic Sample Collection (cont.)

Cohort J: HER2-Negative, Hormone Receptor–Positive Breast Cancer (4-mg GDC-0032 Tablet on a 21-Day on, 7-Day off [21/7] Schedule in Combination with Fulvestrant):



Cohort K: HER-2 Negative, Hormone Receptor–Positive Breast Cancer (4-mg GDC-0032 Tablet on a 5-Day on, 2-Day off [5/2] Schedule in Combination with Fulvestrant):



Cohort L: HER2-Negative, Hormone Receptor–Positive Breast Cancer (4-mg GDC-0032 Tablet on a 7-Day on, 7-Day off [7/7] Schedule in Combination with Fulvestrant):

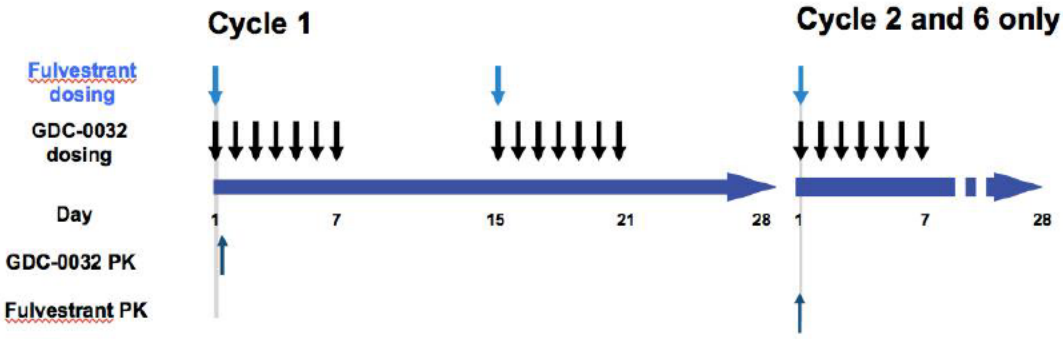
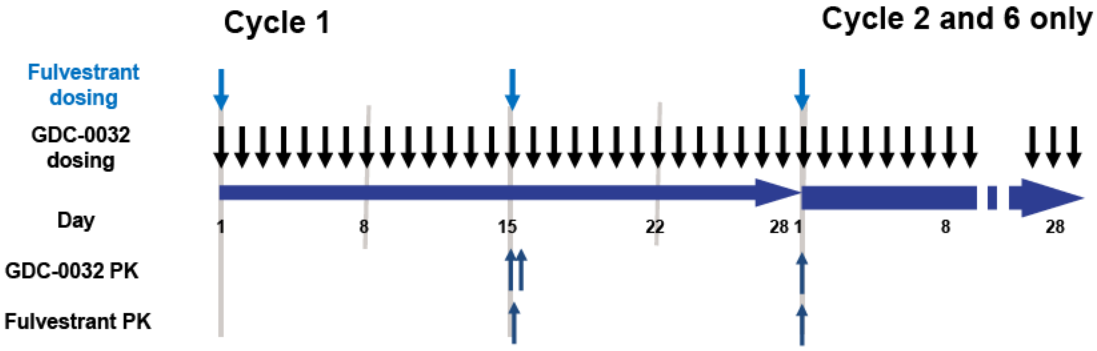
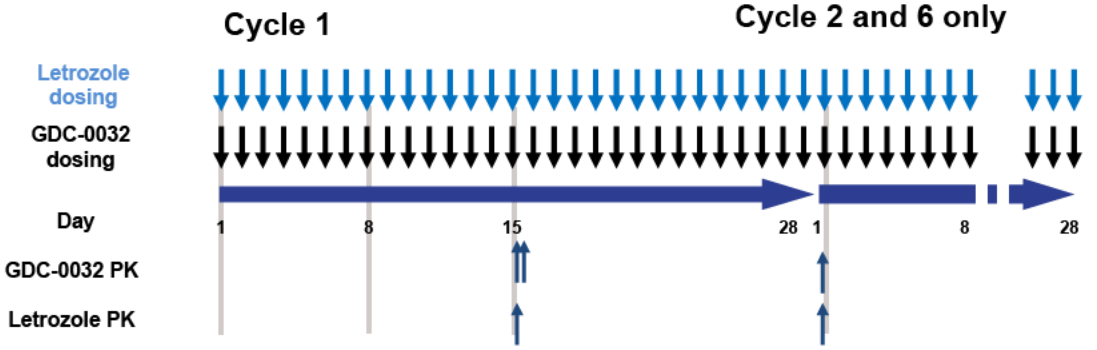


Figure 5 Phase I Stage 2 Dosing and Pharmacokinetic Sample Collection (cont.)

Cohort M: HER2-Negative, Hormone Receptor–Positive Breast Cancer (2-mg GDC-0032 Tablet Daily Dosing Schedule) in Combination with Fulvestrant:



Cohort N: HER2-Negative, Hormone Receptor–Positive Breast Cancer (2-mg GDC-0032 Tablet Daily Dosing Schedule) in Combination with Letrozole:



Cohort P: HER2-Negative, Hormone Receptor–Positive Breast Cancer (4-mg GDC-0032 Tablet Daily Dosing Schedule) in Combination with Letrozole:

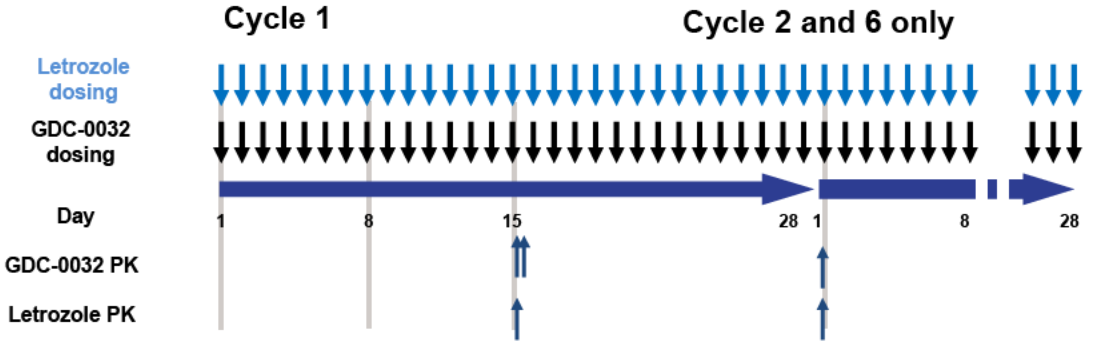
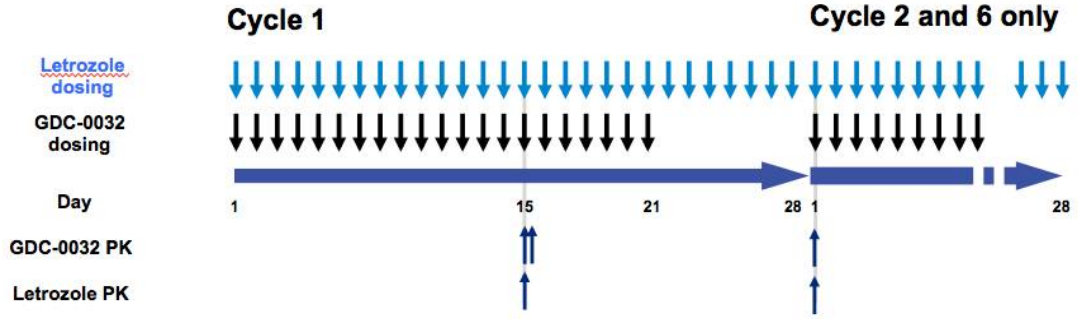
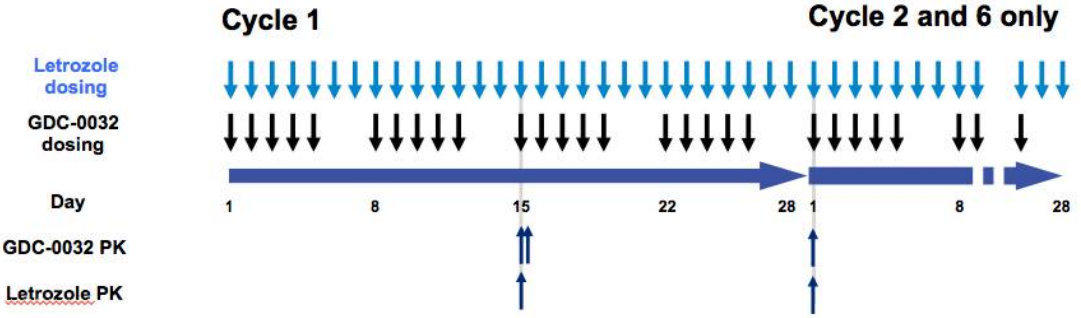


Figure 5 Phase I Stage 2 Dosing and Pharmacokinetic Sample Collection (cont.)

Cohort Q: HER2-Negative, Hormone Receptor–Positive Breast Cancer (4-mg GDC-0032 Tablet on a 21-Day on, 7-Day off [21/7] Schedule) in Combination with Letrozole:



Cohort R: HER2-Negative, Hormone Receptor–Positive Breast Cancer (4-mg GDC-0032 Tablet on a 5-Day on, 2-Day off [5/2] Schedule) in Combination with Letrozole:



Cohort S: HER2-Negative, Hormone Receptor–Positive Breast Cancer (4-mg GDC-0032 Tablet on a 7-Day on, 7-Day off [7/7] Schedule) in Combination with Letrozole:

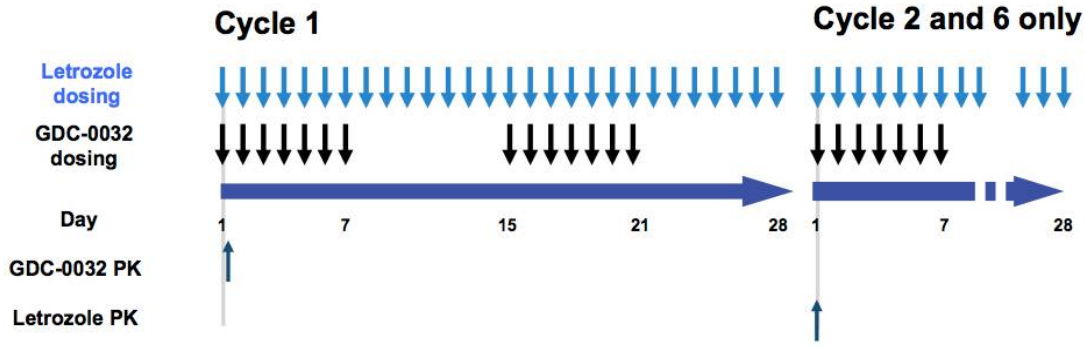
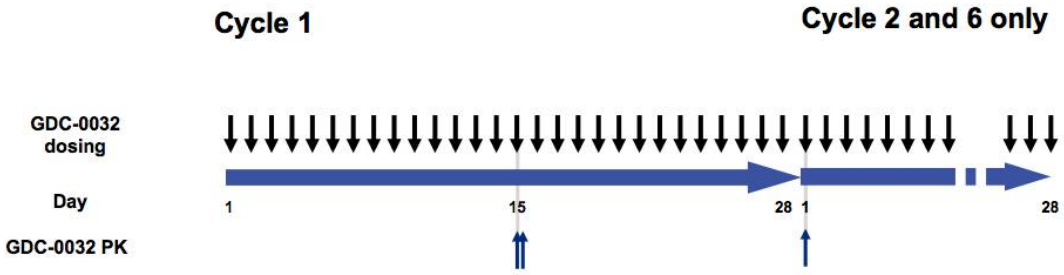
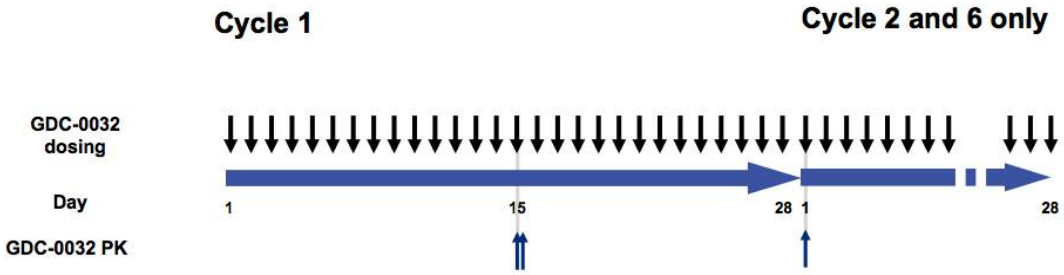


Figure 5 Phase I Stage 2 Dosing and Pharmacokinetic Sample Collection (cont.)

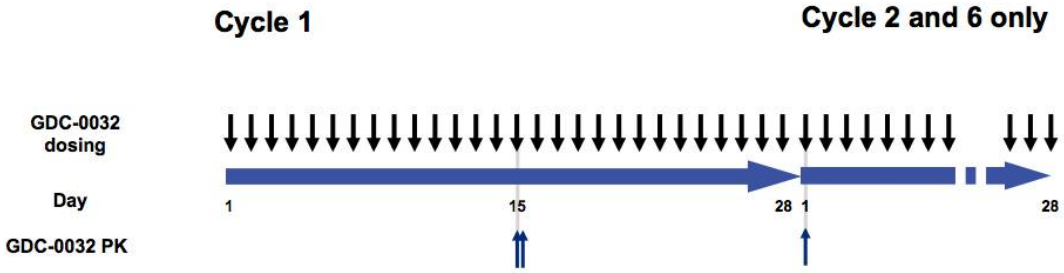
Cohort T: Non-Hodgkin's Lymphoma (4-mg GDC-0032 Tablet Daily Dosing Schedule):



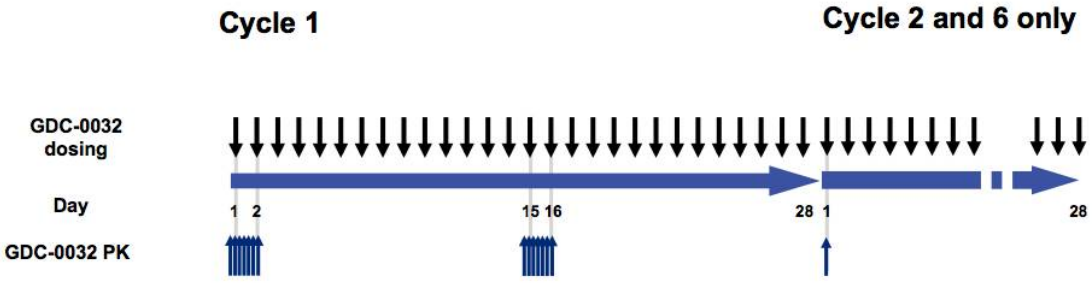
Cohort T2: DLBCL (4-mg GDC-0032 Tablet Daily Dosing Schedule):



Cohort X: *PIK3CA* Mutant Solid Tumors (4-mg GDC-0032 Tablet Daily Dosing Schedule):



Cohort X3: Head and Neck Squamous Cell Carcinoma (4-mg GDC-0032 Suspension Daily Dosing Schedule):



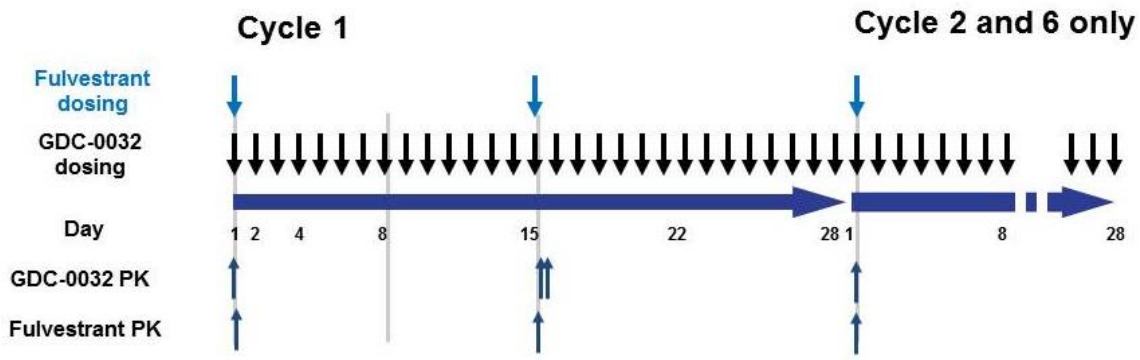
3.1.5 Phase II Portion for GDC-0032 and Fulvestrant

Approximately 60 patients who are postmenopausal with hormone receptor–positive breast cancer will be enrolled to make preliminary assessment of efficacy and to characterize the safety, tolerability, and pharmacokinetics of GDC-0032 in combination with fulvestrant in this patient population. A minimum of 30 of these patients will be required to have *PIK3CA*-mutant breast cancer. Patients enrolled in the Phase II portion will receive GDC-0032 at 6 mg QD in combination with fulvestrant (see Section 3.2.5) based upon results from Stage 1 and Stage 2 of this study.

GDC-0032 and fulvestrant will be administered daily beginning on Cycle 1 Day 1 and will continue for 4 weeks (Days 1-28). Fulvestrant doses do not necessarily need to be held for GDC-0032-related adverse events. GDC-0032 doses do not necessarily need to be held for fulvestrant-related adverse events. See Appendix A-8 for the schedule of assessments and Appendix B-10 for schedule of PK sample collection (see Figure 6).

Based on review of real-time safety and available preliminary PK data from this study with GDC-0032 and fulvestrant, dosing may be halted or modified by the Sponsor as deemed appropriate.

Figure 6 Phase II: Pharmacokinetic Sample Collection to Measure Fulvestrant and GDC-0032 Concentrations



C = Cycle; D = Day; PK = pharmacokinetic.
Note: PK sample collection will be as follows:
GDC-0032: C1D1 predose; C1C15 predose and 4 hours postdose; C2D1 predose; C6D1 predose.
Fulvestrant: C1D1 predose; C1D15 predose; C2D1 predose; C6D1 predose.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Patient Group Selection in Stage 1

The patient population (patients with locally advanced or metastatic solid malignancy that has progressed or failed to respond to at least one prior regimen or for which there is no standard therapy) for this study has been selected primarily to assess the safety and pharmacokinetics of GDC-0032 in patients who would provide the best information

for future studies with GDC-0032. Hematologic malignancies and primary malignancies of the brain or spinal cord are excluded from the Phase I Stage 1 portion of the study. While PI3K pathway activation has been implicated in hematologic malignancies, the potential for bone marrow toxicities with GDC-0032 may make this drug less safe for a first-in-human study in this patient population and may make it difficult to attribute toxicities to disease or the introduction of this agent.

3.2.2 Rationale for Starting Dose and Schedule and Dose-Escalation Rules in Stage 1 of Phase I

The maximum recommended starting dose (MRSD) for the proposed Phase I trial was calculated after evaluation of all the relevant toxicity data and is aligned with current regulatory guidance (DeGeorge et al. 1998; U.S. FDA 2002; ICH S9 2010).

Considering the STD_{10} in rats was determined to be 3 mg/kg QD (18 mg/m^2 QD), one-tenth of the rat STD_{10} in dogs, on a milligram per meter squared (mg/m^2) basis, was not severely toxic to dogs, the rat data formed the basis for the maximum recommended starting dose (MRSD) calculation. A rat-to-human BSA conversion factor of 0.16 and a safety factor of 10 were applied to the STD_{10} in rats, and the resulting MRSD is 0.05 mg/kg or 3 mg QD per 60-kg patient.

At the MRSD of 3 mg QD, the human AUC and C_{max} are projected to be 0.4 μM • hour (193 ng • hour/mL) and 0.02 μM (11 ng/mL), respectively, based on human PK parameters predicted by allometric scaling (maximum lifespan potential (MLP) scaling) (Mahmood and Balian 1996). These values are approximately 89-fold and 215-fold lower, respectively, than the AUC and C_{max} observed in rats at the STD_{10} and 1.5-fold and 5-fold lower, respectively, than the AUC and C_{max} in dogs at the HNSTD.

3.2.3 Rationale for the Pharmacokinetic Evaluation Schedule

The PK evaluation schedule during Cycle 1 is based on the predicted GDC-0032 PK profile in humans using the MLP method of allometric scaling. The half-life ($t_{1/2}$) is predicted to be approximately 14 hours; and time to maximum concentration (T_{max}) is predicted to be approximately 4 to 5 hours postdose.

After a single dose on Day 1, the frequent sampling schedule up to 72 hours is designed to characterize the absorption, distribution, and elimination profile. PK sampling up to 72 hours postdose (~$5 \times t_{1/2}$ after T_{max}) is expected to allow for characterization of the complete PK profile. Urine samples will be collected in Stage 1 up to 24 hours after the dose on Day 1 to determine urinary excretion of GDC-0032.

Steady-state pharmacokinetics of GDC-0032 will be evaluated following the dose on Day 15. Additional blood samples will be taken prior to dosing on Days 8, 22, and 29 during Cycle 1 and at the start of each subsequent cycle (Cycles ≥ 2) to monitor the exposures of GDC-0032 after continuous daily dosing. In addition, PK samples will be

collected on Day 8 in Stage 2, Cohort A for food-effect assessment (see Sections 3.1.4 and 3.2.4).

PK data obtained from patients in early cohorts will be used to determine whether GDC-0032 PK can be adequately characterized with the planned PK sampling schedule. If, upon analysis of these data, it is apparent that the pharmacokinetics of GDC-0032 cannot be adequately characterized with the planned PK sampling schedule, up to four additional samples may be collected from each patient or the PK sampling times may be adjusted. Similarly, sampling time points that are not informative may be eliminated. If changes are made to the PK sampling schedule, revised Appendices B-1 to B-14 will be provided to investigators.

After the plasma and urine samples are analyzed for GDC-0032 concentrations, any leftover samples may be used for exploratory research provided that the patient has specifically consented to this optional research testing.

3.2.4 Rationale for the Food–Effect Analysis in the Stage 2, Cohort A

Co-administration of food may affect the pharmacokinetics of many drugs, including anti-cancer agents (Singh 1999, 2004). Assessments of the effects of food on pharmacokinetics are routinely incorporated in Phase I trials of orally administered oncology drugs (Hoekstra et al. 2005; LoRusso et al. 2005). Drug–food interactions are classified into five categories based on the effect on absorption: no effect, reduced, delayed, increased, or accelerated absorption (Welling 1996).

GDC-0032 appears to be a BCS Class II compound (low and pH-dependent solubility as a weak base, high permeability); these compounds generally have positive food effects in humans (i.e., food increases the exposure of these compounds). Potential food effect on the pharmacokinetics of GDC-0032 will be assessed in Stage 2, Cohort A (see Section 4.3.2).

3.2.5 Rationale for Selection of the Recommended Dose for Future Trials

The recommended daily dose for single-agent GDC-0032 for future trials will be based on safety, tolerability, and PK data. Determination of an adequate dose will require that reasonable exposure consistent with minimal activity in nonclinical models is achieved. In addition, clear evidence of tumor PD modulation would need to be observed at a reasonably tolerated dose. This may be a decrease in downstream PD markers of the PI3K pathway detected in the tumor biopsy, modulation of FDG-PET results supporting an effect on tumor metabolism, or anti-tumor activity as evidenced by tumor marker decreases or tumor shrinkage per RECIST v1.1. The dose and schedule selection will depend on the overall tolerability while maximizing exposure and anticipated effect on PI3K inhibition.

Clinical PK/PD modeling may be conducted to aid the selection of the recommended dose for future trials.

The recommended daily dose for GDC-0032 in combination with endocrine therapy in Phase I, Stage 2, Cohorts E and F will also be based on safety, tolerability, and PK data. In addition, consideration of the patient population that is treated with endocrine therapy will be factored into the dose level chosen. These factors include expected duration of therapy, the overall tolerability in patients who may have a prolonged time to progression, and clinical benefit of the combination. As described in Section 3.1.4, the GDC-0032 dose in Cohorts E and F may be less than the single-agent GDC-0032 dose in Cohorts A–D. Additionally, different schedules and doses of GDC-0032 in combination with endocrine therapy will be evaluated for long-term safety and tolerability in Cohorts J-M for fulvestrant and Cohorts N-S for letrozole.

3.2.6 Rationale for Dosing beyond Cycle 1

Patients who comply with the requirements of the protocol, are tolerating GDC-0032, and have not experienced signs or symptoms of disease progression may be offered dosing with GDC-0032 beyond Cycle 1 for up to 5 years, at the discretion of the investigator after a careful assessment and a thorough discussion of the potential risks and benefits with the patient. Patients receiving benefit from GDC-0032 may have the possibility of continued treatment beyond 5 years at Genentech's discretion and provided that GDC-0032 is available. However, if the study is terminated, GDC-0032 may not be offered after study termination (see Section 3.3).

3.2.7 Rationale for Evaluating Patients with PIK3CA-Mutant Solid Tumors Treated with Single-Agent GDC-0032 (Stage 2, Cohorts A, B, H, and X)

In nonclinical models, GDC-0032 has a stronger anti-tumor effect on *PIK3CA*-mutant tumors than on *PIK3CA* wild-type tumors. Activating mutations of *PIK3CA*, which belongs to the Class IA PI3K family, have been observed in a number of different tumor types, including breast cancer (Bachman et al. 2004; Samuels et al. 2004). These activating mutations have been shown to promote growth and invasion in cancer cells, effects that are abrogated by PI3K inhibitors. Preliminary clinical data with GDC-0032 showed a confirmed partial response observed in a patient with hormone receptor–positive, *PIK3CA*-mutant breast cancer in Stage 1, Cohort 2 treated at the 5-mg capsule daily dose of GDC-0032 that was well tolerated. Clinical activity has also been seen in a patient with *PIK3CA*-mutant lung cancer in Cohort 1 treated at the 3-mg capsule daily dose of GDC-0032. Approximately 20 patients with *PIK3CA*-mutant breast cancer in Stage 2, Cohort A and 20 patients with *PIK3CA*-mutant solid tumors other than breast cancer in Stage 2, Cohort B will be enrolled and treated at the recommended dose for future trials in order to obtain preliminary data on the anti-tumor activity of GDC-0032 in tumors with *PIK3CA* mutations. This information will help inform future trials planned for this diagnostic subpopulation. Evaluating 20 patients in Stage 2,

Cohort A will provide a better estimate of the safety profile of single-agent GDC-0032 at the recommended dose for future trials in the breast cancer patient population that has a higher frequency of *PIK3CA* mutations. Evaluating 20 patients in Stage 2, Cohort B, will provide a better estimate of the safety profile of single-agent GDC-0032 at the recommended dose for future trials in a variety of solid tumors in patients that may benefit based upon GDC-0032 nonclinical and preliminary clinical data.

Evaluating 40 patients in Stage 2, Cohort H will provide a better estimate of the safety profile of single-agent GDC-0032 at the recommended dose for future trials on a different schedule of 21 days on and 7 days off in a variety of solid tumors in patients that may benefit based upon GDC-0032 nonclinical and preliminary clinical data. The 21-day on, 7-day off (21/7) schedule may improve overall tolerability as compared to Cohort B, while maintaining anti-tumor activity. Cohort H must include a minimum of 5 patients with cervical cancer (based upon preliminary clinical data, including a confirmed partial response observed in a patient with endocervical cancer in Cohort B) and a minimum of 20 patients with NSCLC tumors (based upon clinical activity with single agent GDC-0032 seen in *PIK3CA*-mutant NSCLC beginning at the 3-mg QD capsule dose level). Cohort H patients will also be non–breast cancer patients since those have been enrolled in Cohort A. In addition, Cohort H patients will be non-colorectal cancer patients. Patients with colorectal cancer frequently have concomitant mutations of other genes in their tumors such as *KRAS* that render the tumors more resistant to GDC-0032. Such patients may be less likely to benefit from single-agent GDC-0032 treatment.

Data from patients treated with GDC-0032 in Cohorts A, B, and H have shown enhanced activity in multiple tumor types with *PIK3CA* mutations, including breast, lung, gynecologic, and head and neck cancers. Preliminary data have also suggested that patients with squamous cancers may benefit from single-agent GDC-0032 treatment, including HNSCC, NSCLC, and endocervical and anal cancers. As of 30 July 2014, in patients with non–breast cancer solid tumors treated with single-agent GDC-0032 in Study PMT4979g, there were individual patients with *PIK3CA*-mutant cervical, non–small cell lung, and vulvar cancers that had a confirmed partial response. In addition, multiple patients with *PIK3CA*-mutant endometrial, head and neck, laryngeal, non–small cell lung, uterine, rectal, squamous cell, or ovarian cancers had a best confirmed response of stable disease (Genentech internal data).

To further identify cancers in which GDC-0032 may have activity, Study PMT4979g has been amended to add Cohort X (“basket” cohort), in which patients with *PIK3CA*-mutant cancers will receive GDC-0032 daily at the 6-mg or 4-mg tablet dose level. The 10 tumor subtypes were selected for the basket cohort on the basis of nonclinical and clinical efficacy data and *PIK3CA*-mutation frequency. These include endometrial, bladder, HNSCC, cervical, gastric/gastroesophageal junction, small-cell lung, triple-negative breast, colorectal (*KRAS* wild-type), squamous, ovarian, and other cancers with *PIK3CA* mutation not otherwise specified (excluding breast, NSCLC, and colorectal).

Patients with colorectal cancer with *KRAS* mutation will be excluded, because *KRAS* mutation may render tumors more resistant to inhibition of the PI3K/AKT/mTOR pathway (Di Nicolantonio et al. 2010). In Study PMT4979g Stage 1, 2 patients with *PIK3CA*-mutant, *KRAS*-mutant colorectal cancer who were treated with GDC-0032 (5-mg and 8-mg capsule daily doses) experienced progressive disease. In Amendment 9, Cohort X6 (SCLC) was removed, but these patients will be allowed to enroll in Cohort X11. In Amendment 9, Cohort X3 was expanded to include an additional 10-20 patients with HNSCC with amplification of the *PIK3CA* gene and no detectable *PIK3CA* somatic mutations. GDC-0032 administration for Cohort X was chosen at the 6-mg tablet daily dose and schedule on the basis of the tolerable safety profile of patients treated with the recommended single-agent equivalent 9-mg capsule daily dose and schedule (see Section 3.2.13 for further details). In Amendment 9, the starting dose of GDC-0032 in Cohort X was changed to 4-mg tablet daily dose (see Section 3.2.33).

3.2.8 Rationale for Assessing the Effect of GDC-0032 on Midazolam Pharmacokinetics (Stage 2, Cohort C)

In vitro studies suggest that GDC-0032 has the potential to induce CYP3A4 (refer to the Investigator's Brochure for details regarding the nonclinical studies).

A preliminary DDI assessment will be conducted in Stage 2, Cohort C, in which the pharmacokinetics of midazolam will be assessed before dosing with GDC-0032 and following multiple doses of GDC-0032. This assessment may help design future clinical trials with treatment combinations (that may have potential CYP3A4 interaction) and concomitant drug inclusion and exclusion criteria with respect to CYP3A4 substrates.

3.2.9 Rationale for Evaluating Patients with HER2-Positive Breast Cancer at the Recommended Dose for Future Trials (Stage 2, Cohort D)

The PI3K signaling pathway is a major downstream effector of receptor tyrosine kinases that stimulate cell proliferation, promote survival, and inhibit apoptosis, such as HER2. PI3K is required for HER2-mediated transformation (Zhao et al. 2006), which suggests a central role for the PI3K pathway in oncogenic HER2-mediated signal transduction. A high frequency of genetic alterations leading to activation of the PI3K pathway (mutations in PI3K [25%–30%] or PTEN loss [22%–27%]) has been observed in breast cancer, including HER2-positive breast cancer (Saal et al. 2005; Berns et al. 2007). In addition, a PI3K inhibitor has been shown to inhibit the proliferation of HER2-positive breast cancer cell lines that are both trastuzumab-sensitive and trastuzumab-resistant (Junttila et al. 2009). A confirmed partial response has also been observed in a patient with hormone receptor–positive, HER2-positive, *PIK3CA*-mutant breast cancer in Cohort 2 treated at the 5 mg capsule daily dose of GDC-0032 that was well tolerated. Taken together, these data provide a strong rationale for developing inhibitors of PI3K pathway signaling as a therapeutic strategy for HER2-positive breast cancer.

3.2.10 Rationale for Evaluating Patients with Solid Tumors with Increased PIK3CA Copy Number at the Recommended Dose for Future Trials (Stage 2, Cohort G)

The PI3K signaling pathway is a major downstream effector of receptor tyrosine kinases that stimulate cell proliferation, promote survival, and inhibit apoptosis. A high frequency of genetic alterations can lead to the activation of the PI3K pathway other than PI3K mutation. For instance, increased *PIK3CA* copy number, encoding the p110-alpha subunit of PI3K, occurs in a variety of tumors including squamous cell lung cancer (33%; Yamamoto et al. 2008), head and neck cancer (37%; Pedrero et al. 2005), ovarian cancer (24%; Kolasa et al. 2009), endometrial cancer (12%; Konopka et al. 2011), and gastric cancer (36%; Byun et al. 2003). Increased *PIK3CA* copy number has been associated with PI3K pathway activation in both cell lines and tumors (Shayesteh et al. 1999; Yamamoto et al. 2008; Shi et al. 2012) and a PI3K inhibitor has been shown to inhibit the proliferation of *PIK3CA* amplified cancer cell lines (Shayesteh et al. 1999). Stable disease for 11 months occurred in a patient with squamous lung carcinoma with increased *PIK3CA* copy number who was treated with GDC-0032 daily at the 3-mg capsule dose. Taken together, these data provide a strong rationale for developing inhibitors of PI3K pathway signaling as a therapeutic strategy for tumors with increased *PIK3CA* copy number. Evaluating 20 patients in Stage 2, Cohort G, will provide a better estimate of the safety profile of single-agent GDC-0032 at the recommended dose for future trials in a variety of solid tumors in patients who may benefit based upon nonclinical data and preliminary GDC-0032 clinical data.

3.2.11 Rationale for Evaluating Hormone Receptor–Positive Breast Cancer at the Recommended Dose for Future Trials with Alternate Schedules in Combination With Endocrine Therapy (Stage 2, Cohorts E, F, J–M, and N–S)

Approximately one-third of patients with hormone receptor–positive breast cancer have mutations in *PIK3CA*, the gene encoding the alpha catalytic subunit of PI3K (p110α), and an additional one-fifth of patients have loss of PTEN protein expression (PTEN null). These alterations are generally mutually exclusive in breast cancer tumor samples. Both alterations result in up-regulation of the PI3K pathway (Saal et al. 2005; Stemke-Hale et al. 2008) and sensitize nonclinical models to inhibition by selective PI3K inhibitors. In addition, multiple lines of nonclinical and clinical data support a key role of the PI3K pathway in the generation of resistance to hormonal therapies in patients with breast cancer (Johnston 2009; Osborne and Schiff 2011), making hormone receptor–positive breast cancer a rational indication for PI3K inhibitors. Recent clinical data have also demonstrated an additive clinical benefit of combining the aromatase inhibitor exemestane with everolimus, a rapamycin analogue that inhibits TOR pathway signaling for the treatment of advanced hormone receptor–positive breast cancer (Baselga at al. 2011). Preliminary clinical data with GDC-0032 showed a confirmed partial response observed in a patient with hormone receptor–positive, *PIK3CA*-mutant breast cancer in Cohort 2 treated at the 5 mg capsule daily dose of GDC-0032 that was

well tolerated. Based on the strong scientific rationale and preliminary clinical data for GDC-0032 in hormone receptor–positive breast cancer, the combination of GDC-0032 and endocrine therapy (letrozole or fulvestrant) will be tested.

Letrozole is a non-steroidal aromatase inhibitor and an effective treatment of postmenopausal patients with hormone receptor–positive breast cancer that is relatively well tolerated. The expected toxicities for GDC-0032 and letrozole are not overlapping, as discussed in Sections 3.4.2 and 3.4.7.

Fulvestrant is an estrogen receptor antagonist and an effective treatment of postmenopausal patients with hormone receptor–positive breast cancer that is relatively well tolerated. The expected toxicities for GDC-0032 and fulvestrant are not overlapping, as discussed in Sections 3.4.2 and 3.4.8.

To fully establish a combination with endocrine therapy (letrozole and fulvestrant) with GDC-0032 in a population that might require dosing for longer periods relative to a Phase I patient population, and to obtain a better estimate of less common toxicities such as pneumonitis, enrollment of 20 patients each in Cohorts E and F will establish a robust safety and tolerability profile as these combinations are evaluated in larger subsequent studies (see Section 4.9.10).

It is important to test both combinations as letrozole and fulvestrant have different mechanisms of action, different pharmacokinetic properties, and different potential for DDIs with GDC-0032. A minimum of 10 patients will be required to have *PIK3CA*-mutant breast cancer in each of the cohorts (Cohorts J–M and N–S). In nonclinical models, GDC-0032 has a stronger anti-tumor effect on *PIK3CA*-mutant breast tumors than on *PIK3CA* wild-type tumors. Preliminary clinical data with GDC-0032 showed a confirmed partial response observed in a patient with hormone receptor–positive, *PIK3CA*-mutant breast cancer in Cohort 2 treated at the 5-mg capsule daily dose of GDC-0032 that was well-tolerated.

Initial data from Cohort F (GDC-0032 in combination with fulvestrant) with multiple partial responses at 6-mg capsule QD suggests that this dose has anti-tumor activity. Based upon updated safety data, certain adverse events, such as diarrhea, colitis, and rash, sometimes occur in patients after multiple cycles of treatment. An alternate dosing schedule for GDC-0032 with scheduled intermittent treatment breaks from GDC-0032 may be beneficial in improving the overall tolerability of the regimen and possibly decrease the frequency of toxicities such as gastrointestinal (GI) toxicities or rash. Several cohorts with different dosing schedules of GDC-0032 at the 4-mg tablet dose will be tested. Cohorts J and Q will consist of a 21-day on, 7-day off (21/7) schedule. Cohorts K and R will consist of a 5-day on, 2-day off (5/2) schedule. Cohorts L and S will consist of a 7-day on, 7-day off (7/7) schedule.

3.2.12 Rationale for Evaluating Hormone Receptor–Positive Breast Cancer at 2-mg Tablets (Stage 2, Cohorts M and N)

Preliminary efficacy results from Cohorts E and F have demonstrated that some patients who started at the GDC-0032 6-mg capsule QD dose and then dose-reduced to 3-mg capsule QD have been able to maintain partial responses. Several alternate dose schedules and dose levels will be tested to obtain further data on the relative tolerability of adding intermittent breaks to the GDC-0032 dosing schedule and of a lower continuous GDC-0032 dosing with endocrine therapy. Patients in Cohorts M and N will be administered daily doses of 2-mg GDC-0032 in tablet formulation (equivalent to 3-mg capsule). Data from this dose level will help characterize the risk/benefit profile of the 2-mg tablet in combination with letrozole or fulvestrant.

3.2.13 Rationale for Implementing GDC-0032 in Tablet Form for Cohorts H–X

The impact of formulation on the pharmacokinetics of GDC-0032 has been assessed in the multipart study of healthy volunteers, Study GP28619. See Section 1.3.2 and the Investigator's Brochure for more details. AUC and C_{max} for the 2-mg GDC-0032 tablet were comparable to the 3-mg capsule formulation. A 4-mg GDC-0032 tablet dose is estimated to provide an AUC equivalent to a 6-mg capsule dose because of the linear, dose-proportional pharmacokinetics over a broad dose range demonstrated by GDC-0032. Similarly, a 6-mg GDC-0032 tablet dose is estimated to be equivalent to a 9-mg capsule dose. See Table 1.

Table 1 Dose Conversion between GDC-0032 Capsules and Tablets

Current capsule dose	3 mg	6 mg	9 mg
Tablet dose	2 mg	4 mg	6 mg

3.2.14 Rationale for Assessing the Pharmacokinetics of GDC-0032 in Combination with Letrozole (Stage 2, Cohorts E and N–S)

Letrozole 2.5 mg will be administered orally on a daily schedule. Letrozole is mainly metabolized to a pharmacologically-inactive carbinol metabolite by CYP2A6 and CYP3A4 in vivo. The carbinol metabolite is subsequently excreted by the kidney as a glucuronide conjugate. GDC-0032, which has the potential to induce CYP3A4, may affect the pharmacokinetics of letrozole, thereby resulting in a decrease in letrozole exposure (refer to the Investigator's Brochure for details regarding the nonclinical studies).

Samples for assessing GDC-0032 and letrozole pharmacokinetics will be collected following continuous concomitant daily dosing. The PK data from the combination will be compared with GDC-0032 PK data from this clinical trial and published letrozole PK data.

The purpose of this assessment is to inform study designs of future studies with the combination of GDC-0032 and letrozole.

3.2.15 Rationale for Assessing the Pharmacokinetics of GDC-0032 in Combination with Fulvestrant (Stage 2, Cohorts F, J, K, L, and M; Phase II)

Fulvestrant 500 mg will be administered intramuscularly on Days 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (i.e., every 28 days). Metabolism of fulvestrant appears to involve combinations of a number of possible biotransformation pathways, including oxidation, aromatic hydroxylation, and conjugation with glucuronic acid and/or sulphate. Fulvestrant has not been shown to cause clinically relevant DDIs. Although fulvestrant appears to be a CYP3A4 substrate, concomitant administration with ketoconazole or rifampicin has not had an impact on fulvestrant PK. Therefore, a PK interaction is not expected when fulvestrant and GDC-0032 are given concomitantly.

Samples for assessing GDC-0032 and fulvestrant pharmacokinetics will be collected following administration of the combination.

The purpose of this assessment is to provide information for the design of future studies with the combination of GDC-0032 and fulvestrant.

Given the low likelihood for a DDI between GDC-0032 and fulvestrant, sparse blood samples will be collected in the Phase II portion of the study. The sparse sampling approach will allow for comparison of GDC-0032 and fulvestrant in this slightly different cancer patient population to historical values.

3.2.16 Rationale for Evaluating Patients with Non-Hodgkin's Lymphoma (Stage 2, Cohort T)

The goal of Cohort T is to obtain a preliminary safety assessment of GDC-0032 in patients with non-Hodgkin's lymphoma. See Section 1.4.1.2 for rationale.

3.2.17 Rationale for the Patient Population for Phase II Portion

Female patients with HER2-negative, ER-positive, locally recurrent, or metastatic breast cancer 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. Recently, everolimus was approved by the FDA and European Medicines Agency (EMA) in combination with exemestane for the treatment of advanced or metastatic breast cancer in patients after recurrence or progression following treatment with a nonsteroidal aromatase inhibitor (AI). PI3K-inhibitors are central regulators of the mTOR signaling pathway, and nonclinical findings show that PI3K-inhibitors and dual PI3K-mTOR inhibitors induce a greater amount of apoptosis than everolimus in estrogen-deprived in vitro models (Sanchez et al. 2011); therefore, it is hypothesized that PI3K-inhibitors may be active and demonstrate tumor shrinkage in this setting.

In the Phase II portion of this study, the patient population will include patients with progressive disease during or after treatment with an AI for recurrent or progressive disease. This will enable the evaluation of this regimen in a clinically meaningful population given the new indication for everolimus.

Based on nonclinical and clinical data for GDC-0032 in *PIK3CA* mutant breast cancer, a minimum of 30 patients in the Phase II portion will be required to have *PIK3CA* mutant breast cancer. This will be important to assess the clinical activity in this specific diagnostic subpopulation that may be more likely to benefit from the combination of GDC-0032 and fulvestrant.

3.2.18 Rationale for Assessing the Safety and Efficacy of GDC-0032 in Combination with Fulvestrant (Phase II Portion)

Preliminary data from Stage 2, Cohort F is promising with 3 patients in the 6-mg capsule cohort demonstrating greater than 30% decrease by RECIST. However, patients in Stage 2, Cohort F are heterogeneous in the type and number of prior therapies. Many of these patients have been treated with prior fulvestrant and have had multiple prior chemotherapies. In order to better assess whether the GDC-0032 is tolerable for a longer duration in combination with fulvestrant and to better assess the clinical activity of this combination, a Phase II portion of the study is planned.

The Phase II portion will be different from Stage 2, Cohort F in that no prior fulvestrant will be allowed, and a maximum of one prior cytotoxic chemotherapy for the metastatic setting will be allowed. This patient population will be similar to those to be tested in future studies. Preliminary data on response rate and CBR will be obtained and compared with historical control of fulvestrant.

In addition to a preliminary evaluation of efficacy, the Phase II portion of the study will be important in evaluating the long-term tolerability of GDC-0032 with fulvestrant. Additional safety data can be gathered because patients will be expected to be on study treatment for a longer duration than those in Stage 2, Cohort F.

3.2.19 Rationale for Selection of the Recommended GDC-0032 Dose in Combination with Fulvestrant for the Phase II Portion

The recommended GDC-0032 dose in combination with fulvestrant for the Phase II portion of the trial will be 6-mg capsule QD. This is based upon a comprehensive assessment of GDC-0032 nonclinical and clinical data. In Stage 1, GDC-0032 has demonstrated single-agent activity in breast cancer at 5 mg QD. In Stage 2, the selected single-agent dose was 9-mg capsule QD. Data from Stage 2, Cohorts E and F have provided clinical data for GDC-0032 in combination with endocrine therapy. No DLTs have been observed in Cohort E (GDC-0032 and letrozole) or Cohort F (GDC-0032 and fulvestrant) at the 6-mg and 9-mg dose levels ($n = 6$ for each dose level in each cohort). Preliminary data from Stage 2, Cohort F is promising with 3 patients in the 6-mg capsule cohort demonstrating greater than 30% decrease by RECIST.

The recommended Phase II dose for GDC-0032 in combination with fulvestrant is also based upon the target patient population. Endocrine therapy, including fulvestrant, is relatively well tolerated by patients and has a relatively favorable safety profile. Based on an assessment of the safety, pharmacokinetics, and clinical activity of single-agent GDC-0032 and combination therapy with endocrine therapy agents, the recommended Phase II dose of GDC-0032 in combination with fulvestrant is 6-mg capsule QD.

3.2.20 Rationale for QT/QTc Assessments

The potential of non-cardiovascular drugs to delay cardiac repolarization, which may cause cardiac arrhythmias such as torsade de pointes (TdP), has emerged as a major concern for sponsors and regulators. Recently, two International Conference on Harmonisation (ICH) guidelines for nonclinical (S7B) and clinical (E14) testing have been developed.

Cardiovascular toxicity assessments were incorporated in nonclinical studies conducted with GDC-0032 on the basis of the testing strategy outlined in the ICH S6 and S7B guidelines. Results from these studies suggest that GDC-0032 is unlikely to cause delayed cardiac repolarization, prolongation of the QT/QTc interval, or arrhythmias. GDC-0032 inhibited the hERG channel in a GLP functional assay with an $IC_{50} = 136$ μM, which is $>$ 27,000-fold higher than the predicted unbound C_{max} at 3 mg, the starting dose in Stage 1 of this Phase I clinical trial, and is not considered to pose a cardiovascular risk based on Redfern et al. 2003.

Transient increases of 13–18% in arterial blood pressure (systolic, diastolic, and mean pressures) observed in telemetry-instrumented dogs administered 0.3 and 1.0 mg/kg were reversed after 5 hours postdose and were not considered to be adverse.

In the 28-day GLP toxicity study in dogs, a decreased heart rate and, as a consequence, increased PR interval (external ECGs) was noted in animals administered 0.3 and 1 mg/kg, respectively, on Study Day 28 but not during the recovery phase and therefore not considered adverse. Furthermore, these effects were not observed in the GLP single-dose cardiovascular safety pharmacology study in telemetry-instrumented dogs that were administered the same doses. Taken together, these observed effects on heart rate and PR interval in the 28-day study are considered to be minimal, reversible, and non-adverse. ECGs will be done in triplicate during the study. Furthermore, patients will be monitored for potential cardiovascular effects as part of standard safety monitoring procedures.

The QT/QTc assessment strategy for this trial was based on recommendations in the ICH E14 guideline and the special considerations for evaluating drug effects on the QT/QTc interval in cancer patients (Fingert and Varterasian 2006). Triplicate digital ECGs will be collected at baseline and postdose on Day 1 and Day 15 for Stage 1 patients. Additional ECGs will be collected during steady-state exposure in Stage 2 (e.g., after 2 weeks of continuous dosing). ECGs at different timepoints will be collected

concurrently with PK sampling to allow for an evaluation of the relationship between GDC-0032 exposure and changes in QT/QTc interval. Meal intake relative to dosing and other factors (e.g., supine position, ECGs collected before PK sampling) will be standardized, as it is well established that numerous external factors such as these may prolong the QT/QTc interval (Bednar et al. 2001).

The timing of ECG collections was based on the PK profile of GDC-0032 in humans predicted from allometric scaling of nonclinical PK data and a typical small-molecule PK profile. The collection schedule should allow for an adequate characterization of the QT/QTc interval over a range of GDC-0032 concentrations. If the observed PK profile is different from the predicted PK profile, up to four additional ECGs may be collected from each patient or the ECG measurement times may be adjusted. Likewise, measurement times that are not informative will be eliminated.

3.2.21 Rationale for FDG-PET Evaluation

In vitro, GDC-0032 has been shown to inhibit glucose uptake in tumor cells, and similar experiments are underway to confirm this effect in tumor xenografts using FDG-PET imaging. The PI3K pathway has demonstrated an impact on the Glut1 transporter; thus, change in glucose uptake may be a valid PD marker (Shaw and Cantley 2006). In addition, FDG-PET has been demonstrated to be a useful tool to identify early changes associated with tumor activity (Weber 2006). Decreases in tumor FDG uptake have been observed in a clinical trial in which patients were treated with the PI3K-inhibitor GDC-0941. Significant changes in tumor FDG uptake in patients treated with GDC-0032 will provide evidence that this agent is able to exert biologic effects in tumor tissue and will aid in the selection of the dose to be used in future studies. See Section 4.5.1.g for details on FDG-PET imaging and Appendix G for details regarding assessments of FDG-PET response.

3.2.22 Rationale for Surrogate Pharmacodynamic Samples

Surrogate PD assays are routinely incorporated into Phase I oncology trials to determine whether an investigational agent can modulate the drug target in humans and to explore the various relationships between exposure of the agent, surrogate biomarkers, and other study endpoints (LoRusso et al. 2005). Evaluation of changes in PD markers such as pAKT in easily accessible blood samples may provide support for the effects of GDC-0032 in modulating the PI3K pathway. Evaluation of changes in circulating angiogenic factors may provide additional evidence for the effects of GDC-0032 in modulating tumor angiogenesis. Collection of multiple samples at different GDC-0032 exposures may allow a better understanding of the relationship between pharmacokinetics and pharmacodynamics.

3.2.23 Rationale for Pharmacogenetic Blood Sample Collection

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 a potentially drug-related rash, diarrhea, and/or colitis safety assessments (including but not limited to human leukocyte antigen [HLA]). 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, affecting their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase (UGT) 1A1, which facilitates the metabolism and excretion of SN-38 (the active metabolite of irinotecan), are at higher risk for adverse effects associated with the use of standard doses of irinotecan (O'Dwyer 2006). Preliminary results from in vitro metabolism studies with GDC-0032 suggest that GDC-0032 is partially metabolized by multiple phase I cytochrome P450 enzymes, including CYP3A4. 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 will be collected from all patients in this study for potential pharmacogenetic analysis of genes that may affect the pharmacokinetics of GDC-0032 or the response to GDC-0032.

The decision to analyze the samples will be based on a review of the PK and safety response data.

Most recently, HLA has been demonstrated to play an important role in the development of drug-induced rash for some drugs (carbamazepine, abacavir, and allopurinol). Therefore, evaluation of genetic variants of genes that may regulate the immune response (including but not limited to HLA) may also be investigated to characterize unusual safety responses that are not predicted by GDC-0032 pharmacokinetics.

3.2.24 Rationale for Collection of Archival Tumor Specimens

Development of a predictive diagnostic assay that enables prospective identification of patients who are likely to respond to treatment with GDC-0032 would facilitate the future clinical development of this agent. Both *PIK3CA* mutation and PTEN loss have been shown to be present in multiple tumor types with high frequency. *PIK3CA* chromosomal amplification has also been described to be prevalent in several cancer types. These variations are known to increase proliferative and oncogenic properties and are strong candidates for a predictive diagnostic marker. Archival paraffin-embedded tissue will be used to assay for specific *PIK3CA* mutations by sequencing or quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)–based methods and by

immunohistochemistry (IHC) for loss of PTEN expression. DNA and/or RNA may also be extracted from tumor tissue to enable the identification of somatic mutations and transcript expression levels through technologies such as NGS-based platforms. *PIK3CA* amplification may be assayed using in situ hybridization to determine the number of chromosomal copies of *PIK3CA* in tumor cells or by molecular methods. Other potential predictive markers that are related to the PI3K pathway may also be analyzed if guided by either nonclinical or clinical data. Examples may include tumor type-specific biomarkers, such as BCL2 and MYC in DLBCL and p16 in HNSCC.

3.2.25 Rationale for Collection of Fresh Tumor Specimens

Correlation of pathway inhibition in tumor tissue would be important to confirm an appropriate dose and exposure for GDC-0032 for future studies. Paired tumor tissue biopsies will be optional, both predose and postdose, for all patients, with the exception of 6 patient slots (3 patients with *PIK3CA*-mutant and 3 patients with *PIK3CA*-wild-type tumors) in each of Cohorts N and P, in which paired tumor biopsies will be mandatory. The purpose of these mandatory biopsies is to obtain PD data at different doses of GDC-0032 in combination with letrozole on the PI3K (and other) pathways in both *PIK3CA*-wild-type and mutant tumors. A minimum of 5 patients from Cohort X3 are required to provide fresh pre-treatment and on-treatment biopsy samples to assess the effects of GDC-0032 on PI3K (and other cancer-related) pathways in HNSCC. The pretreatment tissue biopsy will be reviewed by a pathologist to determine whether the tissue is evaluable. If the pretreatment tissue is evaluable, then a subsequent biopsy will be performed either during Cycle 1 or Cycle 2, approximately 1–4 hours after the morning dose, depending on the cohort to which the patient is assigned (see Section 4.5.1.n). Patients will be asked to consent to provide tumor biopsy samples. Tumor biopsies upon progression of disease are also optional and may be informative in understanding the mechanisms of resistance to GDC-0032, including alterations in the PI3K pathway such as *PIK3CA* mutations. Tissue samples will be used to assess PD changes in PI3K pathway (and other) markers, such as pS6 and a group of other downstream markers by IHC assay and the reverse-phase protein array (RPPA) when IHC assay is not available. In addition, alterations of the PI3K pathway, such as PI3K mutation status and PTEN loss by IHC, may be examined. DNA and/or RNA may also be extracted from tumor tissue to enable the identification of somatic mutations and transcript expression levels through technologies such as NGS. These findings will help to determine changes in pathway status relative to archival tissue and any clinical activity observed. If sufficient tissue is available, drug levels within tissue will also be measured.

3.2.26 Rationale for Collection of Blood for DNA Mutation Analysis in Plasma

There is increasing evidence that circulating DNA obtained from blood specimens of cancer patients is representative of the DNA and mutational status of tumor cells (Diehl et al. 2008; Maheswaran et al. 2008). Assays have been developed to identify the

mutations (including *PIK3CA*) in ctDNA from plasma, and results from this analysis will be correlated with both fresh tumor specimens (when available) and archival tumor specimens. Detection of *PIK3CA* or other cancer-related mutations in plasma may be used for disease monitoring.

3.2.27 Rationale for Collection of Blood Sample for the Detection of Circulating Tumor Cells

Tumor cells can be found circulating in the blood of cancer patients. The use of circulating tumor cells (CTCs) as a potential surrogate biomarker of treatment efficacy has been examined in metastatic breast cancer, and prospective trials are ongoing to evaluate the clinical significance of CTCs (Cristofanilli et al. 2004; Moreno et al. 2005; Budd et al. 2006). CTCs can serve as a complement to the characterization of tumor tissue, and there are multiple methods for isolating and characterizing these cells. CTCs have been correlated with HER2 gene amplification by fluorescence in situ hybridization (FISH) (Fehm et al. 2002; Meng et al. 2006). The predominance of a critical number of CTCs with a cancer stem cell phenotype may correlate with disease progression, but this is controversial. Exploratory analyses of CTCs for other proteins and genes involved in the biology of metastases and acquisition of therapy resistance may be examined using various platforms at selected timepoints.

3.2.28 Rationale for Collection of Blood Sample for the Detection of Cytokine and Chemokines in the Plasma

Emerging evidence indicates that increases in levels of systemic cytokines and chemokines, such as receptor tyrosine kinase growth factors, can attenuate response to drugs, particularly targeted agents such as GDC-0032 (Wilson et al. 2012).

3.2.29 Rationale for Suspension (Extemporaneous Formulation) for Patients with Head and Neck Squamous Cell Carcinoma

A significant proportion of patients with HNSCC have disease or undergo surgical procedures that make it difficult for them to swallow food, liquids, and medications. These patients often receive nutrition and medications through gastrostomy tubes. To administer GDC-0032 to these patients, instructions will be provided to patients for extemporaneous preparation of a suspension form of GDC-0032 from tablets, only at sites where administration of the extemporaneous suspension is approved by the IRB/EC (see Section 4.3.2.b). To better understand the pharmacokinetics of GDC-0032 administered as a suspension, additional PK measurements will be obtained from patients in Cohort X3 (Appendix B-10).

3.2.30 Rationale for Cycle 1, Day 8 Visit for Cohort H

As of 23 October 2015, 1 case of Grade 4 hyperglycemia was reported in each of Cohorts H and X. One patient enrolled on Cohort H (GDC-0032 6 mg tablet, 21 days on, 7 days off) had Grade 4 hyperglycemia on Cycle 1 Day 15. One patient enrolled on Cohort X (GDC-0032 6 mg tablet QD) had Grade 4 hyperglycemia on Cycle 1 Day 14.

Both patients achieved glucose control with GDC-0032 dose interruption and management of hyperglycemia per protocol guidelines and were able to resume GDC-0032 dosing.

Because these two cases occurred early in Cycle 1, an additional fasting blood glucose (FBG) check as part of a chemistry panel and clinic visit should be performed at Cycle 1, Day 8 for patients receiving GDC-0032 6 mg tablets (Cohort H). This increased monitoring may help to identify some of the patients at an earlier timepoint who would otherwise develop subsequent severe hyperglycemia. Based upon the 40-hour half-life of GDC-0032, testing for fasting blood glucose after 1 week of continuous dosing and steady-state exposure may identify patients with asymptomatic hyperglycemia (e.g. Grade 2 or 3 hyperglycemia) that could then be managed per protocol guidelines. This additional assessment brings Cohort H in alignment with the schedule of assessments of other cohorts on PMT4979g that have GDC-0032 at 6 mg tablet-equivalent or higher doses and also have a Cycle 1 Day 8 blood glucose check. Based upon the available clinical data and experience with GDC-0032, the glucose monitoring is sufficient for subsequent cycles. The Sponsor believes the current schedule of glucose monitoring is adequate for those patients being treated at the 4-mg tablet dose level.

3.2.31 Rationale for Evaluating NHL using 4-mg Tablets (Stage 2, Cohort T and T2)

As of 18 March 2016, there were 5 of 8 (62.5%) patients who had events of grade 3 or greater neutropenia reported in Cohort T, including one case of febrile neutropenia and one case of neutropenic colitis that were deemed serious in a mixed non-Hodgkin's lymphoma patient population. Initial events of Grade 3 or higher neutropenia occurred during Cycle 1 in 4 of 5 patients with this event. Grade 3 or higher leukopenia (including neutropenia) in other cohorts, including Cohort X, has been an otherwise rare event (at 6 mg: 5/179 [2.8%] and at 4 mg: 3/197 [1.5%]), suggesting that neutropenia following GDC-0032 is mainly seen in patients with hematologic malignancies. Infections and, in some cases, serious infections were also observed in Cohort T, including bacteremia, respiratory tract infection, and one episode of septic shock. To try to reduce the incidence of neutropenia and infection in Cohorts T and T2 NHL patients, the dose of GDC-0032 will be a 4-mg tablet daily, decreased from a 6-mg tablet daily originally utilized in Cohort T. This change in starting dose was implemented in an administrative letter to sites on 25 July 2016. Patients enrolled in Cohorts T and T2 should have a weekly CBC for the first two cycles and on Day 1 of each subsequent cycle or more frequently as clinically indicated. In addition, new neutropenia management guidelines are introduced in Amendment 9 (Section 3.4.5.i).

3.2.32 Rationale for Pneumocystis Jirovecii Pneumonia Prophylaxis in Cohorts T and T2

In response to the recent provisional safety measure recommended by the European Medicines Agency (EMA) for NHL patients treated with the PI3K-delta-specific inhibitor

idelalisib, recommendation for Pneumocystis jirovecii pneumonia (PJP) prophylaxis is introduced in Amendment 9 as a precautionary measure against a possible therapeutic class effect. Recommendations for PJP prophylaxis for patients in Cohorts T and T2 are given in Section 4.4.1.1.

3.2.33 Rationale for Change in Starting Dose from 6 mg to 4 mg in Cohort X

The rationale for this dose change is to obtain safety and efficacy data at the 4 mg dose in patients with PIK3CA-mutant solid tumors in Cohort X. In preliminary analysis of Cohort X, partial responses at 6 mg have been observed in different tumor types, including HNSCC, triple-negative breast cancer, cervical cancer, cholangiocarcinoma, and other tumor types. However, potential differences in tolerability have been observed between Cohort X and other PMT4979g cohorts with lower doses. Overall dose reduction rates in Cohort X are similar to other cohorts, but dose reductions have occurred earlier. As of 12 Aug 2016, in Cohort X, 13 dose reductions in 87 safety-evaluable patients occurred prior to Cycle 2. In the PMT4979g Phase II cohort (4 mg tablet equivalent dose), 2 dose reductions in 60 patients occurred prior to Cycle 2. Numerically higher rates of pneumonitis have been observed in mixed solid tumor patients in Cohort X (4 of 87 [4.6%]), compared to pooled data from breast cancer patients in fulvestrant (4 of 167 [2.4%]) or letrozole (2 of 114 [1.8%]) cohorts. In order to optimize the benefit-risk profile in the Cohort X population, the dose in Cohort X will be lowered from 6 mg to 4 mg for all newly enrolling patients. Patients already enrolled at 6 mg may continue at that dose at the investigator's discretion or may lower the dose to 4 mg in consultation with the Sponsor. In choosing the 4 mg starting dose for Cohort X, efficacy at this dose has been observed in other cohorts, and safety has been manageable. Note that the dose and schedule for Cohort H of GDC-0032 6 mg, 21 days on, 7 days off, will not be changed, because Cohort H is testing an alternative schedule at the 6 mg dose.

3.2.34 Rationale for Collecting Tumor Type–Specific Cancer History and Tumor Pathology

To better understand potential clinical factors associated with response to GDC-0032 in patients with different tumor types (e.g., HNSCC or cervical cancer), the results of local assessments of patient clinical history and tumor pathology will be collected retrospectively. Examples include p16 expression and smoking status in patients with HNSCC and histologic classification in patients with cervical cancer.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measure:

- Incidence of DLTs (as defined in Section 3.1.3.a) by NCI CTCAE v4.0 grade and associated dose of GDC-0032

In addition, the safety will be assessed using the following secondary safety outcome measures:

- Incidence of adverse events by NCI CTCAE v4.0 grade and associated dose of GDC-0032
- Incidence of Grade 3 and 4 abnormalities in safety-related laboratory parameters and associated dose of GDC-0032

3.3.2 Pharmacokinetic Outcome Measures

The following primary PK parameters will be derived from the plasma concentration–time profile of GDC-0032, following administration of single and/or multiple doses, when appropriate as data allow:

- AUC_{inf} after single dose and $AUC_{0-\tau}$ after single and multiple doses
- Maximum plasma concentration (C_{max})
- Minimum plasma concentration (C_{min})
- Time to maximum plasma concentration (t_{max})
- Terminal half-life ($t_{1/2}$)
- Apparent clearance (CL/F) after single and multiple doses
- Accumulation ratio (AR) at steady-state

The following secondary PK parameters may also be derived, when appropriate as data allow:

- C_{max} and AUC under fed and fasted conditions (for patients participating in the food-effect assessment)
- AUC_{0-24hr}, C_{max}, t_{max}, and other PK parameters of midazolam, letrozole, and fulvestrant, when applicable
- Fraction of dose excreted (fe) and renal CL (CLr)
- PK-dose proportionality as assessed with C_{max} and AUC
- The time to achieve steady state as assessed with trough (predose) concentrations

For Phase II

A sparse sampling approach will be used to assess the plasma concentrations of GDC-0032 and fulvestrant following single and multiple doses.

3.3.3 Activity Outcome Measure

The following activity outcome measures will be assessed:

- Best overall response, duration of objective response, and progression-free survival (PFS) for patients with measurable disease according to RECIST v1.1 (see Appendix C)
- In Cohort T, response assessment will be based on the 2007 Revised IWG Response Criteria in Malignant Lymphoma (see Appendix I).

- In Cohort T2, response assessment will be based on a modified version of the 2014 Lugano Response Criteria in Malignant Lymphoma (see Appendix J).

3.3.4 Exploratory Outcome Measures

The following correlative biology outcome measures will be assessed:

- PET response for patients with detectable FDG tumor uptake at baseline (see Section 4.9.9)
- Change from baseline in pAKT levels and/or other pathway biomarkers in platelet-rich plasma (Stage 1 only)
- Change in pS6 level as measured by IHC in patients with accessible tumors who provide consent for biopsy, and, if tissue quantity permits, change in expression or phosphorylation of other PI3-kinase pathway markers, and vascular markers, as measured by IHC and reverse phase protein array (RPPA)
- DNA mutation and copy number status of tumor type- and pathway-specific biomarkers (e.g., *PIK3CA*), RNA expression analysis, and PTEN expression in archival tumor tissue and/or in DNA from blood and in any fresh tumor biopsy samples obtained
- Enumeration of CTCs and assessment of PI3K and cancer-related pathway status, when appropriate, (e.g., *PIK3CA* mutation, PTEN expression, etc.) in CTCs and ctDNA from peripheral blood (Cohorts Q, R, S, T, and X excluded from CTC analysis)
- Expression of cytokines and chemokines in plasma
- QT/QTc interval changes
- Tumor type–specific biomarkers as appropriate; examples may include BCL2 and MYC in DLBCL and p16 in HNSCC.

3.4 SAFETY PLAN

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

3.4.1 Nonclinical Toxicity with GDC-0032

The toxicology program consisted of pilot single- and repeat-dose toxicity studies in rats and dogs, 28-day GLP studies in rats and dogs to support up to 28 QD doses in Phase I trials, GLP cardiovascular, neurobehavioral, and respiratory assessments in vitro and in vivo (rats and dogs), and in vitro genotoxicity studies.

Nonclinical findings were consistent with the anticipated pharmacologic effects of PI3K inhibition and include effects on glucose metabolism, manifestations of lymphoid depletion in tissues, and effects on bone marrow. Additional nonclinical findings included reversible effects on body weights in rats (decreased body weight gain) and in dogs (body weight loss), reversible microscopic formation of cysts in ovaries of rats, and reversible GI inflammation in dogs administered GDC-0032. The majority of findings

was minimal to mild, reversible, and considered not adverse. Moreover, these findings are expected to be clinically monitorable and manageable in patients. Findings from the nonclinical toxicology program are as follows:

- Reversible effects on body weights in rats (decreased body weight gain) and in dogs (body weight loss)
- Dose-dependent increases in blood glucose and insulin in a single-dose glucose challenge test in rats and minimal increases in the 28-day pivotal rat and dog toxicity studies
- Reversible inflammation in dogs (e.g., increased fibrinogen, absolute neutrophil and platelet counts) with neutrophil infiltration in the GI tract in some dogs
- Reversible lymphoid depletion and decreased peripheral blood lymphocytes in rats and dogs
- Reversible bone marrow findings in rats characterized by decreased peripheral blood basophil, eosinophil, and neutrophil counts and microscopic findings of hypocellularity of hematopoietic tissue
- Reversible formation of cyst, with or without hemorrhage, in the corpora lutea in rats
- No adverse cardiovascular, respiratory, neurobehavioral, or ophthalmic abnormalities were detected in vitro and in rat and dog studies
- No clinically-relevant inhibition of hERG was observed in an in vitro assay
- No genotoxic effects were seen in either the human chromosomal aberration study or the bacterial mutagenesis assay.
- No significant responses in an off-target secondary pharmacology screen; high ($>$ 1,000-fold) biochemical selectivity for PI3K-family kinases over other kinases

Based on results of the 28-day rat and dog studies, the STD_{10} in rats was determined to be 3 mg/kg PO QD (18 mg/m^2) and the HNSTD in dogs was determined to be 0.3 mg/kg PO QD (6 mg/m^2). Considering that one-tenth of the rat STD_{10} in dogs, on a mg/m^2 basis, was not severely toxic to dogs, the rat toxicity data formed the basis for the maximum recommended starting dose (MRSD) calculation. A rat-to-human BSA conversion factor of 0.16 and a safety factor of 10 were applied to the STD_{10} in rats, and the resulting MRSD was 0.05 mg/kg or 3 mg QD per 60-kg patient.

3.4.2 Toxicity with PI3K Inhibitors in the Clinic

There are several ongoing clinical trials evaluating PI3K inhibitors. Experience with pan-Class I PI3K inhibitors to date has demonstrated that the agents are generally well tolerated. Common adverse events seen in ongoing clinical trials testing PI3K inhibitors include fatigue, diarrhea, skin rash, altered taste, pneumonitis, and hyperglycemia. In general, these agents appear to be reasonably well tolerated at doses examined to date in the Phase I setting without consistent irreversible and/or unmonitorable toxicities. Certain adverse events (e.g., rash, colitis, and pneumonitis) may also occur after holding or stopping GDC-0032, usually within 1–2 weeks after stopping GDC-0032. See the

Investigator's Brochure for the most current safety data across all GDC-0032 clinical trials, including PMT4979g.

3.4.3 Toxicities Observed with GDC-0032 in Clinical Studies

a. Hyperglycemia

Hyperglycemia has been observed in patients who received GDC-0032 in the single-agent Phase I study. Hyperglycemia has been reversible upon holding GDC-0032 and/or initiation of anti-hyperglycemic medication (e.g., metformin).

Patients with diabetes requiring daily anti-hyperglycemic medication or who have a fasting blood glucose level > 120 mg/dL will be excluded from the study. HbA1c and fasting glucose levels will be monitored at baseline, and additional monitoring of fasting glucose levels during the study will be implemented, as outlined in the schedule of assessments.

b. Rash

Treatment-related rash, including cases of Grade 3 rash, has occurred in patients who received GDC-0032. This rash is commonly manifested as maculo-papular with or without pruritus. Incidence rate and severity of rash appear to be dose dependent. The rash has resolved upon holding of GDC-0032 and/or giving supportive therapy (e.g., topical or systemic steroids).

c. Gastrointestinal Toxicity

Nausea, vomiting, diarrhea, and stomatitis/oral mucositis*, and dyspepsia* have been observed in patients who receive GDC-0032. Colitis was diagnosed by several methods, including endoscopy and abdominal imaging (computed tomography [CT] scans). Pathology from biopsy samples obtained from endoscopy has confirmed colitis. Patients usually present with Grade 2 or Grade 3 diarrhea that has been refractory to antidiarrheals. The time (from the first dose of study treatment) to onset (formal diagnosis of colitis) ranged from approximately 99–250 days. Patients had resolution or improvement of gastrointestinal toxicities upon holding study drug and/or initiating corticosteroid therapy. Perforated duodenal ulcer has been observed in 2 patients (1 patient at 6-mg capsule in combination with letrozole; another patient at 6-mg capsule in combination with fulvestrant). Appropriate caution should be taken with the administration of medications such as aspirin, NSAIDs, and corticosteroids, which can increase the risk of gastritis, peptic ulcers, or GI perforation.

Patients with active inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, are excluded from this study. Patients who resume treatment after hold(s) for gastrointestinal toxicity should be monitored closely for sign of renewed diarrhea.

Dose delay and modification guidelines for patients who experience gastrointestinal toxicities (diarrhea, colitis, and stomatitis/oral mucositis) can be found in Section 3.4.5.d.

d. Pneumonitis

Non-infectious pneumonitis has been observed in patients treated with everolimus and temsirolimus, rapamycin analogues that inhibit mTOR signaling, and PI3K inhibitors.

Pneumonitis has been observed in patients treated with GDC-0032. Symptoms associated with pneumonitis were reversible upon treatment with corticosteroids. As an example, noninfectious pneumonitis has been observed in the single-agent Phase I study in a lung adenocarcinoma patient treated at the 16-mg capsule daily dose level 1 week after discontinuing GDC-0032. The patient was treated with corticosteroids, and associated symptoms resolved.

Refer to Section 3.4.5.b for guidelines on pneumonitis management.

e. Potential Abnormal Liver Enzymes

Some patients have experienced elevations of liver enzymes (e.g., AST or ALT). Patients will be monitored throughout the study treatment for changes in liver enzymes.

Dose delay and modification guidelines for patients who experience elevated liver enzymes can be found in Section 3.4.5.f.

f. Potential Inflammatory or Immunosuppressant Effects

Based on data from nonclinical toxicity studies showing changes in WBC and absolute lymphocyte and/or neutrophil counts, patients will be required to have adequate hematologic function to participate in the study, and any bone marrow toxicities from prior therapies must be resolved before initiation of GDC-0032. Patients will be monitored throughout the study treatment for changes in blood counts and signs of infections.

g. Neutropenia

As of 18 March 2016, there were 5 of 8 (62.5%) patients who had events of grade 3 or greater neutropenia reported in Cohort T, including one case of febrile neutropenia and one case of neutropenic colitis that were deemed serious in a mixed non-Hodgkin's lymphoma patient population. Any grade leukopenia (including neutropenia) in other cohorts, including Cohort X, has been an otherwise rare event (at 6 mg: 5/179 [2.8%] and at 4 mg: 3/197 [1.5%]), suggesting that neutropenia following GDC-0032 is mainly seen in patients with hematologic malignancies. Neutropenia in patients enrolled in Cohort T has been reversible with dose hold and administration of granulocyte colony stimulating factor (G-CSF). Patients will be monitored throughout study treatment for changes in blood counts. Dose delay and modification guidelines for patients who experience neutropenia can be found in Section 3.4.5.i. Infections and, in some cases, serious infections, including bacteremia, respiratory tract infection, and one episode of septic shock, were observed in Cohort T. Patients in Cohorts T and T2 should be monitored closely and evaluated promptly for signs and symptoms of infection.

h. Infections

Infections were identified as an adverse drug reaction during the primary analysis of Study GO29058. At the time of the analysis, of the 416 patients in the GDC-0032 arm, 41.8% had developed infections compared with 23.9% of the 213 patients in the placebo arm. Serious infections occurred in 7.5% of patients in the GDC-0032 arm compared with 0.9% of patients in the placebo arm, and 0.5% of patients died on account of infection in the GDC-0032 arm compared with no patients in the placebo arm. Urinary tract infections were the most commonly reported infection; however, respiratory tract, gastrointestinal tract, and skin infections were also common in the GDC-0032 arm.

Dose delay and modification guidelines for patients who experience infections can be found in Section 3.4.5.j.

i. Additional Adverse Drug Reactions

The following additional adverse drug reactions were identified during the primary analysis of Study GO29058:

- *Alopecia*
- *Fever*
- *Weight loss*

3.4.4 Safety Monitoring of GDC-0032

Safety will be evaluated through the monitoring of all serious and non-serious adverse events, with severity graded according to the NCI CTCAE, v4.0. Safety assessments will include interval history since the previous assessment, physical examination, and specific laboratory studies, including serum chemistries and blood counts (see Appendices A-1 to A-7 *and Appendix A-9* for the schedule of study assessments). Patients in Stages 1 and 2 of the Phase I study will be monitored weekly for safety during the first 9 weeks, then every 2 weeks for an additional 6 months, and every 4 weeks thereafter until 30 days after the last dose of GDC-0032. Patients in the Phase II portion will be monitored for safety per Appendix A-8. Patients with unresolved adverse events thought to be related to GDC-0032 must be followed as clinically indicated, until the event is resolved or stabilized, another anti-cancer therapy is initiated, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the adverse event.

All serious adverse events, Grade 3 or 4 adverse events, and potential DLTs will be reported in real time via the electronic data capture (EDC) system to the Drug Safety representative and Medical Monitor at Genentech. In addition, adverse events will be discussed at regularly scheduled teleconferences between the Medical Monitor and the investigators.

As with any first-in- human study, there is the potential for toxicities that cannot be predicted from animal studies. To mitigate potential unknown risks at least in part, dosing beyond 35 days will be limited to patients who are tolerating GDC-0032 treatment

and not exhibiting signs or symptoms of disease progression, as previously described in Section 3.1. In addition, complete recovery from any prior chemotherapy, radiation therapy, or surgical procedures will be a requirement for study entry. Patients with history of prior pelvic radiation therapy and/or female genital tract fistulae should be carefully monitored for local complications such as bleeding, infection or fistulae. One patient with cervical cancer, on-going rectovaginal fistula, and history of local radiation therapy developed severe localized hemorrhage on study.

The potential for phototoxicity with GDC-0032 is unknown; therefore, it is recommended that patients avoid prolonged sun exposure and apply protective sunscreen and lip balm as appropriate while on study.

Dose escalation to the next higher level will occur following a review of safety data after the last patient completes Cycle 1 in each cohort as well as any safety data obtained from other studies with GDC-0032.

3.4.5 Management of Toxicities

The dose delay and modification instructions provided in Table 2–Table 9 are intended to serve as recommended guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while ensuring 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 treating investigator when deemed to be in the best interest of the patient and to ensure patient safety.

Due to the approximately 40 hour half-life for GDC-0032, investigators should consider holding GDC-0032 for certain Grade 2 toxicities until the adverse events resolves to Grade ≤ 1 as discussed below (e.g., stomatitis/oral mucositis, rash, diarrhea). Certain toxicities can occur within 1–2 weeks of holding or discontinuing GDC-0032 drug (e.g., pneumonitis, colitis, rash). In these cases, the adverse event eventually resolved. Investigators should follow management guidelines for toxicities as described below including administration of topical or systemic corticosteroids as appropriate.

a. Management of Hyperglycemia

Hyperglycemia has been observed in patients who received GDC-0032 while participating in PMT4979g and other studies. Hyperglycemia has been reversible upon holding GDC-0032 and/or initiating anti-hyperglycemic medication (e.g., metformin).

Patients with diabetes who require daily anti-hyperglycemic medication or who have a fasting blood glucose level > 120 mg/dL will be excluded from the study. HbA1c and fasting glucose levels will be monitored at baseline, and regular monitoring of fasting glucose levels will occur during the study. Dose delay and modification guidelines for patients who experience hyperglycemia are presented in Table 2.

Table 2 GDC-0032 Dose Delay and Modification Guidelines for Hyperglycemia

Grade of Hyperglycemia	GDC-0032 Dose Modification and Management Guidelines
1 or 2	Initiation of or an increase in the dose of an anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring will be implemented. GDC-0032 dosing may either be held or continued per investigator evaluation.
3 (asymptomatic)	Hold GDC-0032. Treat hyperglycemia per standard of care, including implementation of additional glucose monitoring and initiation of or an increase in the dose of an anti-hyperglycemic therapy (e.g., metformin). If improves to Grade ≤ 1, may resume GDC-0032 dosing at one dose level lower.
3 (symptomatic), 3 (requiring hospitalization), or 4	Hold GDC-0032. Treat hyperglycemia per standard of care, including implementation of additional glucose monitoring and initiation of or an increase in the dose of anti-hyperglycemic therapy. If improves to Grade ≤ 1, may resume GDC-0032 dosing at one dose level lower. For recurrent symptomatic Grade 3 or Grade 4 hyperglycemic event, GDC-0032 must be permanently discontinued.

b. Management of Pneumonitis

Pneumonitis has been observed in patients treated with GDC-0032. Symptoms associated with pneumonitis were reversible upon treatment with corticosteroids. Dose delay and modification guidelines for patients who experience pneumonitis are presented in Table 3.

Patients who require any daily supplemental oxygen are not eligible for the study. Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment. Oxygen saturation by pulse oximetry will be measured at every visit as part of the assessment of vital signs.

Table 3 Management of Pneumonitis

Grade	Intervention	Investigations	GDC-0032 [a] Dose Adjustment
1	No specific therapy required.	CT scan. Consider PFTs. [b] Repeat CT scan every 8 weeks until return to baseline.	No change.
2	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs and bronchoscopy.	Hold GDC-0032 as long as corticosteroids are being given. If pneumonitis improves to Grade ≤ 1 and upon completion of any corticosteroid treatment, resume GDC-0032 dosing at the same GDC-0032 dose or one dose level lower per investigator evaluation. For recurrent Grade 2 event, resume GDC-0032 dosing at one dose level lower.
3	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated.	CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs. Bronchoscopy is recommended.	Hold GDC-0032 as long as corticosteroids are being given. If pneumonitis improves to Grade ≤ 1 and upon completion of any corticosteroids, resume GDC-0032 dosing at one dose level lower.
4	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated.	CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs. Bronchoscopy is recommended.	Permanently discontinue GDC-0032.

Table modified from White et al. 2010.

CT = computed tomography; PFT = pulmonary function test.

Note: PFTs include tests for DL_{CO} and room air oxygen saturation at rest (pulse oximetry).

[a] Dose reductions per Section 4.3.3.

[b] PFTs may be useful to monitor the effect of interventions such as dose reduction/discontinuation and corticosteroids, in conjunction with imaging (White et al. 2010).

c. Management of Rash

Treatment-related rash is commonly manifested as maculo-papular with or without pruritus. The rash has usually resolved upon holding GDC-0032 and/or giving supportive therapy (e.g., topical or systemic steroids). Dose delay and modification guidelines for patients who experience rash are presented in Table 4.

Table 4 GDC-0032 Dose Delay and Modification Guidelines for Rash

Grade of Rash	GDC-0032 Dose Modification and Management Guidelines
1	Continue dosing at current dose and monitor for change in severity. Consider prescribing topical corticosteroids [a].
2	Hold GDC-0032. Treat rash with topical corticosteroids. Consider treatment of rash with oral corticosteroids [b]. Hold GDC-0032 as long as oral corticosteroids are being administered. If rash improves to Grade ≤ 1and upon completion of any systemic corticosteroids, resume GDC-0032 at the same dose or one dose-level lower per investigator evaluation. For recurrent Grade 2 rash, resume GDC-0032 at one dose level lower.
3	Hold GDC-0032. Treat rash with topical corticosteroids and/or systemic corticosteroids (oral or intravenous). Hold GDC-0032 as long as systemic corticosteroids are being administered. Consider dermatological consultation and skin biopsy. If rash improves to Grade ≤ 1 and upon completion of any systemic corticosteroids, resume GDC-0032 at one dose level lower.
4	Permanently discontinue GDC-0032. Treat with topical corticosteroids and/or systemic corticosteroids. Consider dermatological consultation and skin biopsy.

AE = adverse event; BID = twice daily.

Note: AE grading is based on National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

[a] Suggested topical steroids include hydrocortisone 2.5% to face twice daily, triamcinolone 0.1% or fluocinonide 0.1% cream to body BID.

[b] Suggested oral steroids include methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg × 2 days, 40 mg × 2 days, 20 mg × 2 days, etc.).

d. Management of Gastrointestinal Toxicity

Nausea, vomiting, *dyspepsia,* diarrhea, abdominal pain, stomatitis, and oral mucositis have been observed in patients who received GDC-0032. Colitis was diagnosed by several methods, including endoscopy and abdominal imaging (CT scans). Pathology from biopsies obtained from endoscopy confirmed colitis. Patients usually present with Grade 2 or Grade 3 diarrhea that has been refractory to antidiarrheal agents. The time to onset (from the first dose of study treatment to the formal diagnosis of colitis) ranged from approximately 0.5 to 8 months with a median onset of 4.7 months. Patients had resolution or improvement of gastrointestinal toxicities upon holding study drug and/or initiating corticosteroid therapy. Perforated duodenal ulcer was observed in 2 patients (1 patient at 6-mg capsule dose in combination with letrozole; another patient at 6-mg capsule dose in combination with fulvestrant). Appropriate caution should be taken with

the administration of medications such as aspirin, NSAIDs, and corticosteroids, which can increase the risk of gastritis, peptic ulcers, or gastrointestinal perforation.

Patients with active inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, are excluded from this study. Patients who resume GDC-0032 treatment should be monitored closely for signs of renewed diarrhea.

Dose delay and modification guidelines for patients who experience gastrointestinal toxicities (diarrhea, colitis, stomatitis, and oral mucositis) can be found in Table 5.

Table 5 GDC-0032 Dose Modification and Management Guidelines for Diarrhea and Colitis

Grade	GDC-0032 Dose Modification and Management
1	Manage per standard-of-care with antidiarrheal agents [a] (e.g., loperamide). For Grade 1 diarrhea occurring after Cycle 2 that persists > 5 days despite treatment with antidiarrheal agents, obtain stool culture for infectious workup [b]. Infections (e.g., Clostridium difficile, enteric bacteria, CMV) should be treated with the appropriate antibiotic. For non-infectious diarrhea, consider holding GDC-0032 and treating with a corticosteroid taper (20–40 mg prednisone PO QD starting dose) or budesonide 9 mg PO QD. Upon completion of corticosteroid treatment, resume GDC-0032 dosing at same dose or one dose level lower per investigator evaluation.
2	Hold GDC-0032 and initially manage with antidiarrheal agents [a]. Obtain stool culture for infectious workup [b]. Infections (e.g., Clostridium difficile, enteric bacteria, CMV) should be treated with the appropriate antibiotic. For non-infectious Grade 2 diarrhea that has not improved to Grade ≤ 1 despite 48 hours of antidiarrheal treatment or for Grade 2 colitis, treat with corticosteroid taper (20–40 mg prednisone PO QD starting dose) or budesonide 9 mg PO QD. Steroid dosage can be increased if diarrhea does not improve. If diarrhea or colitis does not improve after 48 hours of corticosteroid treatment, a colonoscopy should be considered to evaluate for other causes of diarrhea (e.g., CMV colitis). If Grade 2 diarrhea occurred after Cycle 2 or improved with corticosteroid treatment or for Grade 2 colitis, resume GDC-0032 dosing at one dose level lower upon improvement to Grade ≤ 1 and after completion of any corticosteroid taper. If Grade 2 diarrhea occurred before Cycle 2 and did not require corticosteroid treatment, resume GDC-0032 dosing at the same dose level or one dose level lower per investigator evaluation upon improvement to Grade ≤ 1. For recurrent Grade 2 diarrhea, resume GDC-0032 dosing at one dose level lower upon improvement to Grade ≤ 1.
3	Hold GDC-0032 dosing and initially manage with antidiarrheal agents [a]. Obtain stool culture for infectious workup [b]. Infections (e.g., Clostridium difficile, enteric bacteria, CMV) should be treated with the appropriate antibiotic. For Grade 3 diarrhea or colitis, treat with systemic corticosteroids (IV methylprednisolone 16–20 mg every 8 hours or prednisone 60–80 mg PO QD equivalent to start). Can increase steroid dosage if diarrhea does not improve. Consider colonoscopy as part of further gastrointestinal workup. If diarrhea does not improve after 48 hours of corticosteroid treatment, a colonoscopy should be considered to evaluate for other causes of diarrhea (e.g., CMV colitis).

Table 5 GDC-0032 Dose Modification and Management Guidelines for Diarrhea and Colitis (cont.)

Grade	GDC-0032 Dose Modification and Management
3	If diarrhea or colitis improves to Grade ≤ 1 and upon completion of any steroid taper, resume GDC-0032 dosing at one dose level lower. Patients with recurrent Grade 3 diarrhea or colitis must be permanently discontinued from GDC-0032.
4	Permanently discontinue GDC-0032. Manage as per Grade 3 diarrhea guidelines.

CMV = cytomegalovirus; IV = intravenous; PO = taken by mouth; QD = once daily.

[a] Suggested antidiarrheals include the following:

- Loperamide (initial: 4 mg, followed by 2 mg after each loose stool, up to 16 mg/day)
- Diphenoxylate and atropine (diphenoxylate 5 mg, four times daily, until control achieved [maximum: 20 mg/day], then reduce dose as needed; some patients may achieve control with doses of 5 mg/day)
- Tincture of opium (6 mg of undiluted opium tincture [10 mg/mL] four times daily).

[b] Non-infectious diarrhea can be diagnosed by stool culture with work-up for Clostridium difficile and for various enteric bacteria. Fecal calprotectin is a possible marker for bowel inflammation. Blood-based CMV polymerase chain reaction test can also be used to detect CMV infection.

e. Management of Stomatitis and Oral Mucositis

Aggressive mouth care for oral mucositis and stomatitis with mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) may also be helpful in managing symptoms, and it is recommended that these are implemented with early signs of dry mouth, Grade 1 mucositis, or Grade 1 stomatitis (see Table 6). Examples of mouth care include rinsing with nonalcoholic mouthwash, flossing after each meal, using a mild toothpaste and soft-bristled toothbrush, and avoiding agents that contain hydrogen peroxide, iodine, and thyme derivatives. It may also be helpful to advise patients to avoid foods that are spicy, acidic, or salty.

Table 6 GDC-0032 Dose Delay and Modification Guidelines for Stomatitis and Oral Mucositis

Grade	GDC-0032 Dose Modification and Management Guidelines
All grades	Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, anti-fungal and/or antibiotics) may be implemented to help manage symptoms. Diet management (e.g., avoidance of spicy foods)
1	Monitor symptoms and initiate management (see above). Re-evaluate within 48–72 hours.
2	Hold GDC-0032 and manage until Grade ≤ 1. If stomatitis or mucositis improves to Grade ≤ 1, resume GDC-0032 dosing at the same dose or one dose level lower per investigator evaluation. For recurrent Grade 2 stomatitis or mucositis, resume GDC-0032 dosing at one dose-level lower.
3	Hold GDC-0032 and manage until Grade ≤ 1. If stomatitis or mucositis improves to Grade ≤ 1, resume GDC-0032 dosing at one dose-level lower.
4	Permanently discontinue GDC-0032.

f. Management of Abnormal Liver Enzymes

Some patients have experienced elevations of liver enzymes (e.g., AST or ALT). Patients will be monitored throughout the study treatment for changes in liver enzymes. Given the potential for hepatic toxicity, all patients must have adequate liver function as manifested by measurements of serum bilirubin and hepatic transaminases for initial and continued dosing. Separate criteria for eligibility, continued dosing, and DLT are given for patients with hepatic metastases and Grade 2 hepatic transaminase levels at baseline to allow safety testing to be adequately assessed in this patient group.

For new abnormal liver enzymes (e.g., elevated AST or ALT), a standard clinical work-up to understand the etiology of the abnormality should take place per local guidelines. In many cases, elevated liver enzymes may be a result of liver metastases, concomitant medications, or biliary obstruction. Dose delay and modification for patients who experience abnormal liver enzymes can also follow the guidelines in Table 9 if deemed clinically appropriate by the investigator.

g. Management of Asymptomatic Lipase and/or Amylase Elevations

Some patients treated with GDC-0032 have experienced asymptomatic lipase and/or amylase elevations in blood tests without any clinical or radiographic symptoms of pancreatitis or another clear etiology for the abnormal lab values. Upon discussion with Medical Monitor and after a risk-benefit assessment, investigators can consider continuing GDC-0032 therapy in such patients at the same dose or one dose level lower. Investigators should have a low threshold for interrupting GDC-0032 for any concerning clinical gastrointestinal toxicities.

h. Potential Inflammatory or Immunosuppressant Effects

On the basis of GDC-0032 data from nonclinical toxicity studies showing changes in WBC and absolute lymphocyte and/or neutrophil counts, patients will be required to have adequate hematologic function to participate in the study, and any bone marrow toxicities from prior therapies must be resolved before initiation of GDC-0032. Patients will be monitored throughout the study treatment for changes in blood counts and signs of infection.

Infection prophylaxis and recommendations for Pneumocystis prophylaxis are covered in Section 4.4.1.1.

i. Management of Neutropenia

Some patients with hematologic malignancies in Cohort T have experienced grade 3 and higher neutropenia, including cases of febrile neutropenia and one case of neutropenic colitis. Patients enrolled in Cohorts T and T2 should have a weekly CBC for the first two cycles and on Day 1 of each subsequent cycle or more frequently as clinically indicated. While the clinical experience is limited, neutropenia has responded to dose interruption and/or administration of daily G-CSF (filgrastim), with a median duration of approximately 3 days. Dose delay and modification guidelines for patients who experience neutropenia are presented in Table 7.

Table 7 Neutropenia Management Guidelines

Grade (ANC × 1000/mm^3)	Management
1 (< LLN–1500)	Continue current GDC-0032 dosing.
2 (< 1500–1000)	Continue current GDC-0032 dosing.
3 (< 1000–500)	Options: 1) Hold GDC-0032 and suggest GCSF per local guidelines until ANC > 1000. 2) Continue GDC-0032 and administer GCSF until ANC > 1000, then re-check CBC in 2–3 days. Monitor CBC at least weekly.
4 (< 500)	Stop GDC-0032 dosing until ANC > 1000. Start GCSF per local guidelines until ANC > 1000. Monitor CBC at least weekly. May re-challenge at same dose after ANC > 1000 if asymptomatic Grade 4. If symptomatic Grade 4 neutropenia (e.g. febrile neutropenia or active infection), or recurrent Grade 4 asymptomatic neutropenia, resume GDC-0032 at next lower dose. If neutropenic colitis or recurrent Grade 4 symptomatic neutropenia, may consider resuming at next lower dose or stopping treatment, depending on individualized assessment of benefit-risk.

ANC = absolute neutrophil count; CBC = complete blood count; GCSF = granulocyte colony stimulating factor; LLN = lower limit of normal.

j. Management of *Infection and* Other Clinically Significant Adverse Events

Investigators and patients should be aware of the increased risk of infection with GDC-0032. If a diagnosis of infection is made, appropriate treatment should be promptly initiated and consideration should be given to holding or discontinuing GDC-0032 as per the guidelines in Table 8.

See Table 8 for the dose modifications for other clinically significant adverse events.

Table 8 GDC-0032 Dose Delay and Modification Guidelines for Other Clinically Significant Adverse Events

Grade	GDC-0032
3: first event	Hold GDC-0032 until Grade ≤ 1. Consider restarting at next lower dose.
3: recurrent 4: non-life-threatening	Hold GDC-0032 until Grade ≤ 1. Restart at next lower dose.
4: life-threatening	Permanently discontinue GDC-0032.

3.4.6 Safety Monitoring for Midazolam

Midazolam is a relatively fast-acting benzodiazepine with central nervous system (CNS)-depressant effects. It is frequently used perioperatively for sedation, anxiolysis, and amnesia. Significant potential side effects include respiratory depression, apnea, and airway obstruction. The severity and frequency of these events are markedly increased when midazolam is combined with other CNS-depressing agents as well as in patients with abnormal airway anatomy, cyanotic congenital heart disease, or sepsis or severe pulmonary disease. In some cases, death or hypoxic encephalopathy has occurred.

In this study, a single oral dose of midazolam 5 mg will be given as part of the assessment of potential DDIs with GDC-0032. This dose is similar to that typically given in the perioperative setting. The effects of midazolam are dependent on the dose, route of administration, and the presence or absence of other medications, especially those with CNS effects. The time to onset of sedative effects following oral administration is approximately 30 minutes and recovery may take 2–6 hours.

The single dose of midazolam 5 mg used in this study will be given while patients are under medical supervision in the clinic for safety and PK assessments. Patients will remain in clinic and/or another appropriate medically-supervised setting until the effects of midazolam have subsided and patients may be safely discharged.

3.4.7 Safety Monitoring for Letrozole

Letrozole is a nonsteroidal aromatase inhibitor indicated for first-line treatment of hormone receptor–positive or hormone receptor–unknown, locally advanced or metastatic breast cancer in postmenopausal women. Letrozole is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

The most frequently reported adverse events in a first-line breast cancer clinical trial with letrozole were bone pain, hot flushes, back pain, nausea, arthralgia, and dyspnea. Discontinuations for adverse events other than progression of tumor occurred in 2% of

patients on letrozole. Refer to the letrozole Package Insert or Summary of Product Characteristics for additional information.

There are no expected significant overlapping toxicities between GDC-0032 and letrozole. Routine safety monitoring and periodic laboratory tests for the letrozole and GDC-0032 combination will occur throughout the study.

3.4.8 Safety Monitoring for Fulvestrant

Fulvestrant is an estrogen receptor antagonist indicated for the treatment of hormone receptor–positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

In a trial with postmenopausal patients 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 were injection-site pain (11.6% of patients), nausea (9.7%), and bone pain (9.4%). 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 Summary of Product Characteristics (SmPC).

There are no expected significant overlapping toxicities between GDC-0032 and fulvestrant. Routine safety monitoring and periodic laboratory tests for the fulvestrant and GDC-0032 combination will occur throughout the study.

3.5 DOSING CONSIDERATIONS

Dosing beyond Cycle 1 for Phase I and II patients will be allowed at the discretion of the investigator after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Only those patients who are tolerating GDC-0032 treatment and are not exhibiting signs and symptoms of disease progression may receive GDC-0032 beyond Cycle 1. Patients must comply with the requirements of the protocol. These patients will have the opportunity to continue study treatment as long as the above conditions are met. Efforts will be made to allow patients to continue treatment if they are continuing to benefit, depending on the development status and availability of GDC-0032. If the study is terminated however, study drug may not be offered after termination (see Section 4.7).

3.6 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with the U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), applicable local, state, and federal laws, as well as applicable country laws and regulations.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Patient Selection

Specific inclusion and exclusion criteria for Phase I (Stage 1 and Stage 2) cohorts are detailed in Section 4.1.2 and Section 4.1.3, respectively. There is no limit to the number or type of prior regimens for Phase I patients.

4.1.2 Inclusion Criteria

Patients must meet the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Phase I, Stage 1 and Stage 2, Cohorts A–D, G, H, T, T2, and X: Histologically documented locally advanced or metastatic solid malignancy or non-Hodgkin's lymphoma that has progressed or failed to respond to at least one prior regimen and are not candidates for regimens known to provide clinical benefit
- Phase I, Stage 2, Cohorts A–X will include patients with the following tumor type, mutational status, and cohort-specific inclusion criteria:

  Cohort A: Patients with *PIK3CA*-mutant breast cancer based on results from archival or fresh tumor tissue

  Cohort B: Patients with *PIK3CA*-mutant solid malignancy other than breast cancer, based on results from archival or fresh tumor tissue

  Cohort C: Patients with any type of solid malignancy

  Cohort D: Patients with HER2-positive breast cancer (e.g., FISH-positive, chromogenic in situ hybridization [CISH]-positive, IHC 3+, or HER2-positive by local laboratory assessment)

  Cohorts E and F: Postmenopausal patients with histologically documented locally advanced or metastatic hormone receptor–positive breast cancer that has progressed or failed to respond to at least one prior endocrine therapy in the adjuvant or metastatic setting. A minimum of 10 patients per cohort will be required to have *PIK3CA*-mutant breast cancer.

  Hormone receptor-positive is defined as expression of ER in ≥ 1% cells, or hormone receptor-positive by local laboratory or regional definition.

  Postmenopausal is defined as one of the following:

  1. Age ≥ 60 years
  2. Age < 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment; these patients must have discontinued gonadotropin-releasing hormone (GnRH) agonists at least 15 months prior to initiation of study treatment

3. Prior bilateral oophorectomy (≥ 28 days prior to first treatment on Day 1 of Cycle 1)

Cohort G: Patients with solid malignancy with increased *PIK3CA* copy number, based on archival or fresh tumor tissue

Cohort H: Patients with *PIK3CA*-mutant solid malignancy other than breast or colorectal cancer, based on results from archival or fresh tumor tissue

Must include a minimum of 5 patients with cervical cancer and a minimum of 20 patients with NSCLC

Cohorts J, K, L, M, N, P, Q, R, and S: Postmenopausal patients with HER2-negative, hormone receptor–positive breast cancer as defined in Stage 2, Cohort F that has progressed or failed to respond to at least one prior endocrine therapy in the adjuvant or metastatic setting. HER2-negative will be as defined by local clinical guidelines.

For each of these cohorts, a minimum of 10 patients per cohort will be required to have *PIK3CA*-mutant breast cancer. Hormone receptor–positive defined as expression of ER in ≥ 1% cells, or hormone receptor–positive by local laboratory or regional definition. HER2-negative will be as defined by local clinical guidelines.

For Cohorts N and P, a minimum of 6 patients (3 patients with *PIK3CA*-mutant and 3 patients with *PIK3CA*-wild-type tumors) in each cohort must consent to undergo paired pre-treatment and on-treatment tumor biopsies.

As per national or local treatment guidelines, endocrine therapy (e.g., fulvestrant, letrozole) is recommended and treatment with cytotoxic chemotherapy is not necessary for patients at time of entry into the study.

Cohort T: Patients with non-Hodgkin's lymphoma, regardless of *PIK3CA* mutation status

Cohort T2: Patients with DLBCL, regardless of *PIK3CA* mutation status

Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of DLBCL and for exploratory research on candidate biomarkers.

All Cohort T2 patients must consent to providing a formalin-fixed paraffin-embedded block or a minimum of 15 freshly cut, unstained tumor slides (submission of 20 is strongly encouraged) from archival tumor tissue or a newly collected ("fresh") tumor sample for *PIK3CA* mutation testing as well as for other protocol-mandated exploratory assessments. Lymph node excisions or biopsies are strongly preferred.

If archival tissue is unavailable or unacceptable, a pretreatment core-needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

If the available biopsy was performed more than 12 months prior to Day 1 of Cycle 1 for patients with DLBCL or the patient received anti-lymphoma treatment between the time of the most recently available biopsy and Day 1 of Cycle 1, a core-needle biopsy is strongly recommended.

Further details are provided in Section 4.5.1.v.

Cohort X: Patients with *PIK3CA*-mutant tumors based on results from archival or fresh tumor tissue, with tumor histology defined for the following sub-cohorts:

X1: endometrial cancer

X2: bladder cancer

X3: HNSCC

10–20 patients with *PIK3CA* mutant HNSCC, regardless of *PIK3CA* copy number status, by local or central testing

10–20 patients with HNSCC with amplification of the *PIK3CA* gene and no *PIK3CA* somatic mutations detected, by local or central testing

A minimum of 5 patients in Cohort X3 must consent to undergo paired pre-treatment and on-treatment tumor biopsies.

X4: cervical cancer

X5: gastric and gastroesophageal junction cancer

X6: small cell lung cancer (closed)

X7: triple-negative (HER2-negative, ER-negative, PR-negative) breast cancer, as defined by local guidelines

X8: colorectal cancer, excluding *KRAS* mutant

X9: squamous cell cancer, excluding any histology in Cohorts X1–X8 and X10 and NSCLC

X10: ovarian cancer, including clear cell

X11: *PIK3CA*-mutant cancer not otherwise specified in Cohorts X1–X10 and excluding breast, NSCLC, and colorectal cancer. SCLC is allowed in Cohort X11.

Cohort X patients may be enrolled on the basis of local or central test results that indicate a *PIK3CA* mutation or amplification. A copy of the local *PIK3CA* gene mutation or amplification report must be submitted for review by the Medical Monitor prior to enrollment.

All Cohort X patients must consent to providing a formalin-fixed paraffin-embedded 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 *PIK3CA*-mutation and copy number testing as well as for other protocol-mandated exploratory assessments. When tissue is available from more than one source

(e.g., primary tumor or metastatic sites), preference should be given to the tissue that was most recently collected.

Tumor tissue should be of good quality based on total and viable tumor content (refer to the Laboratory Manual). Evaluation of the patient's tumor sample for adequate tumor-tissue content by a central laboratory must occur prior to initiation of study treatment.

For Cohort X8, determination of *KRAS* wild-type status is required prior to initiation of study treatment per local institutional guidelines or central testing.

- Evaluable or measurable disease per RECIST v1.1 (see Appendix C) for Phase I (Stages 1 and 2, except Cohorts T, T2, and X) and Phase II and/or the following for Phase I (Stages 1 and 2) only:

  Patients with castrate-resistant prostate cancer with non-measurable disease are eligible if they have two rising prostate-specific antigen (PSA) levels $\geq$ 5 ng/mL measured $\geq$2 weeks apart that meet the PSA Working Group criteria for progression prior to initiation of study treatment (see Appendix D), and otherwise are not candidates for regimens known to provide clinical benefit.

  Ovarian cancer patients with non-measurable disease are eligible if they have progression or recurrence based on serum CA-125 levels as defined by the Gynecological Cancer Intergroup (GCIG) Criteria for Evaluation according to CA-125 (see Appendix E), and otherwise are not candidates for regimens known to provide clinical benefit.
- Evaluable or measurable disease for Cohorts T and T2 patients with lymphoma of at least one bi-dimensionally measurable lesion on CT scan defined as $>$ 1.5 cm in its longest diameter
- For Cohort X, measurable disease per RECIST v1.1 (see Appendix C)
- Phase II: Postmenopausal female patients with HER2-negative, hormone receptor–positive breast cancer as defined in Stage 2, Cohort F. A minimum of 30 patients are required to have *PIK3CA*-mutant breast cancer. For Phase II, HER2-negative will be as defined by local clinical guidelines.

  HER2 status will be identified by an IHC and/or an ISH assay as evaluated at the institution.
- Phase II: As per national or local treatment guidelines, endocrine therapy (i.e., fulvestrant) is recommended, and treatment with cytotoxic chemotherapy is not necessary for patients, at time of entry into the study.
- ECOG performance status of 0 or 1 at screening (see Appendix F)
- Life expectancy of $\geq$ 12 weeks
- Adequate hematologic and organ function within 28 days prior to initiation of study treatment, defined by the following:
- Granulocyte count $\geq$ 1500/μL

- Hemoglobin $\geq$ 9 g/dL
- Platelet count $\geq$ 100,000/μL (except for Cohorts T and T2 where platelet count $\geq$ 75,000/μL)
- Fasting glucose $\leq$ 120 mg/dL
- Total bilirubin $\leq 1.5 \times$ ULN
- Patients with known Gilbert's disease who have serum bilirubin $\leq 3 \times$ ULN may be enrolled.
- Serum albumin $\geq$ 2.5 g/dL
- AST and ALT $\leq 1.5 \times$ ULN with the following exception:

  Patients with documented liver metastases may have AST and/or ALT $\leq 5.0 \times$ ULN.
- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation:

  $$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$
- International normalized ratio (INR) $< 1.5 \times$ ULN and activated partial thromboplastin time (aPTT) $< 1.5 \times$ ULN
- For patients requiring anticoagulation therapy with warfarin, a stable INR between 2–3 is required. If anticoagulation is required for a prosthetic heart valve, then INR should be between 2.5–3.5.
- Documented willingness to use an effective means of contraception (e.g., abstinence, hormonal or double barrier method, surgically sterilized partner; if using hormonal means of contraception, then a second means of contraception must be used) for both men and women while participating in the study and for 90 days after the last dose of GDC-0032
- Willingness to provide archival tumor tissue

4.1.3 Exclusion Criteria

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

- Leptomeningeal disease as the only manifestation of the current malignancy
- Type 1 or 2 diabetes requiring anti-hyperglycemic medication
- Inability or unwillingness to swallow pills, except for patients with HNSCC (Cohort X3)

  Patients with head and neck cancer with gastrostomy tubes are eligible to take GDC-0032 as a suspension, only at sites where administration of the extemporaneous suspension is approved by the IRB/EC.
- Malabsorption syndrome or other condition that would interfere with enteral absorption

- Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants for symptomatic control)

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

  Disease outside the CNS is present.

  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

  Minimum of 2 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade ≥ 3) acute toxicity with no ongoing requirement for $\geq$ 10 mg of prednisone per day or an equivalent dose of other corticosteroid
- Congenital long QT syndrome or QTc $>$ 500 msec
- Active congestive heart failure or ventricular arrhythmia requiring medication
- Uncontrolled ascites requiring weekly large-volume paracentesis for 3 consecutive weeks prior to initiation of study treatment
- Active infection requiring intravenous (IV) antibiotics
- Patients requiring any daily supplemental oxygen
- Active inflammatory diseases that require immunosuppressants, including small or large intestine inflammation such as Crohn's disease or ulcerative colitis

  Patients currently receiving immunosuppressants (e.g., sulfasalazines) are considered to have active disease and are, therefore, ineligible.
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Known human immunodeficiency virus (HIV) infection
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications (examples include but are not limited to clinically significant non-healing wound, active bleeding, or ongoing fistula or active tuberculosis infection)
- Significant traumatic injury within 3 weeks prior to initiation of GDC-0032
- Major surgical procedure within 4 weeks prior to initiation of GDC-0032
- Treatment with chemotherapy, corticosteroids, hormonal therapy (except GnRH agonists or antagonists for prostate cancer, or oral endocrine therapy),

immunotherapy, or biologic therapy as cancer therapy within 3 weeks prior to initiation of study treatment.

Note: For Cohorts T and T2, if corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg/day prednisone or equivalent can be given for $<$ 7 days, but all tumor assessments must be completed prior to start of corticosteroid treatment.

- Oral endocrine therapy (e.g., tamoxifen, letrozole, anastrozole, exemestane) within 2 weeks prior to initiation of study treatment.

  Note: Patients who are receiving letrozole prior to study entry may continue letrozole treatment if they are enrolled into a Stage 2 letrozole combination cohort (Cohorts E, N, P, Q, R, and S).

- Kinase inhibitors, approved by regulatory authorities, may be used up to 2 weeks prior to initiation of GDC-0032, provided that any drug-related toxicity has completely resolved and prior approval is obtained from the Medical Monitor.
- Prior treatment with a PI3-kinase inhibitor in which the patient experienced a Grade $\geq$ 3 drug-related adverse event or otherwise would be at increased risk for additional PI3K-related toxicity
- For patients in Stage 2 (Phase I) and Phase II: prior treatment with PI3-kinase inhibitors, except for Cohorts T and T2 (e.g., prior idelalisib is allowed for Cohorts T and T2)
- For patients in Stage 2, Cohorts J, K, L, and M and in Phase II: prior treatment with fulvestrant
- For patients in Stage 2, Cohorts, J, K, L, M, N, P, Q, R, and S and patients in Phase II: Prior treatment with $>$ 1 cytotoxic chemotherapy regimen in the metastatic setting (Prior treatment with everolimus is permitted and is not considered a cytotoxic chemotherapy)
- For Cohort T: Patients with primary CNS lymphoma, acute leukemias, accelerated/blast-phase chronic myelogenous leukemia, CLL, Burkitt lymphoma, plasma cell leukemia, or non-secretory myeloma
- For Cohort T2: Patients with prior history of Richter's transformation or allogeneic stem cell transplantation. Prior autologous stem cell transplantation is allowed.
- Palliative radiation to bony metastases within 2 weeks prior to initiation of GDC-0032
- Radiation therapy (other than palliative radiation to bony metastases) as cancer therapy within 4 weeks prior to initiation of GDC-0032
- Treatment with an investigational agent within 3 weeks or 5 half-lives prior to initiation of GDC-0032, whichever is shorter
- Unresolved toxicity from prior therapy, except for alopecia and Grade 1 peripheral neuropathy
- Pregnancy or lactation

- Women of childbearing potential (including those who have had a tubal ligation) must have a documented negative pregnancy test within 28 days prior to initiation of GDC-0032.
- Inability to comply with study and follow-up procedures

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. Patients in Stage 1 will be assigned to dose levels in the order in which they are enrolled. Patients in Stage 2 will be assigned by Genentech. Patients in Phase II will be assigned by Genentech. Patients in Cohort X (Basket Cohort) will be assigned to a tumor sub-cohort (X1–X11) on the basis of their tumor type by Genentech. Upon completion of all screening evaluations and verification that the patient has met all eligibility criteria, sites will contact Genentech to confirm patient eligibility and to obtain a patient number, cohort and dose assignment, and confirm the dosing schedule.

4.3 STUDY TREATMENT

4.3.1 Formulation and Storage

a. GDC-0032

GDC-0032 Drug Product is provided in a capsule formulation consisting of active pharmaceutical ingredient (API) powder (at different quantities) and hard gelatin capsule shells. The Drug Product will be initially provided as capsules of three strengths: 1 mg, 3 mg, and 5 mg. The 1-mg capsules are size 3 and Swedish orange, the 3-mg capsules are size 2 and white opaque, and the 5-mg capsules are size 2 and dark green. The only excipient in GDC-0032 Drug Product is the hard gelatin capsule shell.

The Drug Product is packaged in high-density polyethylene (HDPE) bottles. Each bottle is induction sealed and labeled for clinical use.

GDC-0032 capsules will be shipped to the study sites in bulk containers. GDC-0032 capsules should be stored at room temperature between 59–86°F (15–30°C) and should be protected from light. Patients will be instructed to store study drug at room temperature between 59–86°F (15–30°C).

GDC-0032 is also provided for use in clinical studies as a white, film-coated, immediate-release tablet formulation of 2 mg strength. GDC-0032 tablets should not be stored above 25°C.

Patients with gastrostomy tubes who are unable to swallow tablets may receive their GDC-0032 dose in the form of a suspension prepared extemporaneously from (GDC-0032) 2-mg tablets. Patients will be provided with instructions for preparation of the suspension. See Section 4.3.2.b.

For further details, see the Taselisib (GDC-0032) Investigator's Brochure.

b. Midazolam (Stage 2, Cohort C Only)

Refer to the midazolam Package Insert or SmPC for details on the formulation and storage of midazolam.

c. Letrozole (Stage 2, Cohorts E, N, P, Q, R, and S)

Refer to the letrozole (e.g., Femara®) Package Insert or SmPC for details on the formulation and storage of letrozole.

d. Fulvestrant (Stage 2, Cohorts F, J, K, L, and M; Phase II)

Fulvestrant is supplied in sterile single-patient prefilled syringes containing 50 mg/mL fulvestrant as a 5-mL injection. Refer to the fulvestrant (e.g., FASLODEX®) Package Insert or SmPC for details on the storage of fulvestrant.

4.3.2 Dosage and Administration

The starting dose of GDC-0032 is 3 mg (capsule formulation) in the dose-escalation Phase I, Stage 1 portion. Dose escalations will occur as described in Section 3.1.3.

On Day 1 of Cycle 1 for patients in Phase I, Stage 1 and Stage 2, Cohorts A–G, GDC-0032 will be administered to patients in a clinical setting that can accommodate frequent blood draws over a period of up to 72 hours after the morning dose is administered. See Sections 4.3.2.a and 4.3.2.b for the Stage 1 and Stage 2 dosing regimens, respectively.

At each study visit, after establishing patient eligibility for continued administration of GDC-0032, a sufficient number of capsules or tablets should be dispensed to the patient to last only until the next visit or, at the investigator's discretion, through one cycle. Patients will self-administer GDC-0032 as detailed below, except on study visit days when the GDC-0032 will be administered in the clinic.

Patients will receive a single dose of GDC-0032 on scheduled dosing days. Patients will take GDC-0032 at the same time of day ± 2 hours, unless otherwise instructed. Patients will be instructed as to the number and strength of capsules or tablets to take, according to their assigned dose level and schedule. Patients with head and neck cancer and with gastrostomy tubes who are enrolled in Cohort X3 will be provided with special instructions on how to prepare a suspension (extemporaneous formulation) from GDC-0032 tablets for easier administration (see Section 4.3.2.b). To minimize the number of capsules or tablets administered, doses will be rounded so that a combination of no more than two different strengths will be required. The capsules should never be opened. Patients will be asked to record the time and date that they take each dose in a medication diary.

For Stage 1, unless otherwise instructed, GDC-0032 should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal), except on days of extensive PK sampling (Days 1 and 15 of Cycle 1) when administration will be under

fasted conditions. For administration under fasted conditions, patients will fast overnight for at least 10 hours before dosing and 4 hours postdose and will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of GDC-0032 administration when the capsules will be swallowed whole (not chewed) with 240 mL (8 fluid ounces) of water.

For Stage 2 cohorts, GDC-0032 may be taken with or without food except on days on which there is a post-dose PK assessment where administration should be under fasted conditions. There is no water restriction around the time of GDC-0032 administration under fasted conditions for Stage 2 cohorts.

If a patient misses a GDC-0032 dose or vomits up a capsule or tablet, he or she should be instructed to skip that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up. Patients will be instructed to bring their medication diary to each study visit for assessment of compliance. Patients will also be instructed to bring all unused capsules or tablets to each study visit or, at the investigator's discretion, at the end of each cycle, for GDC-0032 accountability.

On safety assessment days, PK samples will be collected at the same time as other blood tests are performed, including fasting lipid panels. Patients will be instructed to hold the morning dose of GDC-0032 until after PK blood samples have been obtained. For Cohorts H–X, once fasting blood draws have been collected and GDC-0032 administered, the patient need not continue to remain fasted for any post-dose, PK blood draw.

a. Stage 1 Dosing

In Stage 1, Cycle 1 will be 35 days in length and will begin with a PK evaluation, during which all patients will receive a single fasting dose of GDC-0032 on Day 1 at their assigned dose level. The initial dose will be followed by a 7-day washout and frequent PK sampling up to 72 hours to determine the single-dose PK properties of GDC-0032 in humans. Urine samples will be collected up to 24 hours after the first dose to determine urinary elimination of GDC-0032. Blood samples will be taken at several scheduled timepoints to explore the surrogate PD response after a single dose. In Cycle 1, continuous GDC-0032 daily dosing will begin on Day 8 and will continue for 4 weeks (Days 8–35).

Subsequent cycles will be 28 days in length (4 weeks of daily dosing with GDC-0032).

b. Stage 2 Dosing

The dosing regimens for the Stage 2 cohorts are as follows:

- Cohort A: In Cycle 1, patients will receive a single dose of GDC-0032 on Day 1, and then daily doses from Day 8 to Day 35. On Day 1 or 8 of Cycle 1, GDC-0032 administration will be under either fasted or fed conditions for the food-effect assessment (i.e., fasted on Day 1 and fed on Day 8 or vice versa). The patients will

fast overnight for at least 10 hours before the morning dose. If the patient is receiving a high-fat breakfast, the meal must be entirely consumed within ≤30 minutes and GDC-0032 dose will be given 30 minutes after the start of the meal. The high-fat meal (approximately 800 to 1000 calories) will consist of approximately 33 g protein, 58 g carbohydrate, and 75 g fat, respectively (e.g., 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash-brown potatoes, and 8 ounces of whole milk). Patients will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of 240 mL (8 fluid ounces) water intake required for administration of GDC-0032. GDC-0032 capsules will be swallowed whole (not chewed) with water. No additional food should be allowed for at least 4 hours postdose. In addition, patients will receive a GDC-0032 dose under fasted conditions on Cycle 1, Day 22 for assessment of steady state pharmacokinetics. Subsequent cycles will be 28 days in length (4 weeks of daily dosing with GDC-0032).

- Cohorts B, D, and G: In Cycle 1, patients will receive daily oral doses of GDC-0032 on an empty stomach (i.e.,1 hour before or 2 hours after a meal) on Days 1–28, except on Days 1, 8, and 15 when patients receive GDC-0032 under fasted conditions. For subsequent cycles patients will receive daily oral doses of GDC-0032 on Days 1–28.
- Cohort C: In Cycle 1, patients will receive midazolam 5 mg in hydrochloride syrup on Days 1 and 16. Each midazolam dose will be administered by oral syringe, followed by approximately 200 mL of water to rinse the mouth and swallow. Midazolam will not be mixed with any liquid before ingestion. Patients will then receive daily doses of GDC-0032 on Days 2–29. All doses will be taken on an empty stomach (i.e., 1 hour before or 2 hours after a meal), except on Days 1 and 16 when patients receive the doses under fasted conditions. For subsequent cycles patients will receive daily oral doses of GDC-0032 on Days 1–28.
- Cohort E: In Cycle 1, patients will receive daily oral doses of GDC-0032 and letrozole 2.5 mg orally on Days 1–28. Patients will take the GDC-0032 and letrozole doses on an empty stomach (i.e., 1 hour before or 2 hours after a meal), except on Days 1 and 15 when patients will receive the doses under fasted conditions. For subsequent cycles patients will continue to take daily oral doses of GDC-0032 and daily oral doses of letrozole 2.5 mg on Days 1–28. On study visit days, GDC-0032 and letrozole will be administered in the clinic.
- Cohort F: In Cycle 1, patients will receive daily oral doses of GDC-0032 on Days 1–28. Patients will take the GDC-0032 doses on an empty stomach (i.e., 1 hour before or 2 hours after a meal), except on Days 1 and 15 when patients will receive the doses under fasted conditions. Fulvestrant is supplied in sterile single-patient prefilled syringes containing a 250 mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–28 and will receive fulvestrant via intramuscular injections as described above in the clinic on Day 1 of each cycle.

- Cohort H: In Cycle 1, patients will receive daily oral doses of GDC-0032 on Days 1–21 of each 28-day cycle. For PK testing on Cycle 1 Day 15, patients will receive GDC-0032 under fasted conditions in the clinic. For subsequent cycles patients will receive daily oral doses of GDC-0032 on Days 1–21 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic.
- Cohort J: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–21. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. Fulvestrant will be supplied in sterile single-patient prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–21 of each cycle and will receive fulvestrant as described above in the clinic on Day 1 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic.
- Cohort K: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–5, 8–12, 15–19, and 22–26. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. Fulvestrant will be supplied in sterile single-patient prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–5, 8–12, 15–19, and 22–26 of each cycle and will receive fulvestrant as described above in the clinic on Day 1 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic.
- Cohort L: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–7 and 15–21. For PK testing on Cycle 1 Day 1, patients will take GDC-0032 under fasted conditions in the clinic. Fulvestrant is supplied in sterile single-patient prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–7 and Days 15–21 of each cycle and will receive fulvestrant via intramuscular injections as described above in the clinic on Day 1 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic.
- Cohort M: In Cycle 1, patients will receive a daily oral dose of 2 mg GDC-0032 in tablet form on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. Fulvestrant is supplied in sterile single-patient, prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1-2 minutes per injection) as two 5-mL

injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles, patients will continue to receive daily oral doses of GDC-0032 on Days 1–28 and will receive fulvestrant via intramuscular injections, as described above, in the clinic on Day 1 of each cycle. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic.

Fulvestrant dosing exceptions (Cohorts F, J, K, L, and M): For patients with moderate hepatic impairment (Child-Pugh Class B), a single-agent dose of 250 mg is recommended on the basis of clinical data described in the fulvestrant package insert.

- Cohort N: In Cycle 1, patients will receive a daily oral dose of 2 mg GDC-0032 in tablet form and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 and letrozole doses under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily oral doses of GDC-0032 and daily oral doses of letrozole 2.5 mg on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 and letrozole will be administered in the clinic.
- Cohort P: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 and letrozole under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily oral doses of GDC-0032 and daily oral doses of letrozole 2.5 mg on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 and letrozole will be administered in the clinic.
- Cohort Q: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–21 and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily oral doses of GDC-0032 on Days 1–21 and daily oral doses of letrozole 2.5 mg on Days 1–28. For PK testing on Day 1 of Cycle 2 and 6, GDC-0032 and letrozole will be administered in the clinic.
- Cohort R: In Cycle 1, patients will receive a daily oral dose of 4 mg GDC-0032 in tablet form on Days 1–5, 8–12, 15–19, and 22–26 and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 and letrozole under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily oral doses of GDC-0032 on Days 1–5, 8–12, 15–19, and 22–26 of every cycle and daily oral doses of letrozole 2.5 mg on Days 1–28. For PK testing on Day 1 of Cycle 2 and 6, GDC-0032 and letrozole will be administered in the clinic.

- Cohort S: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form on Days 1–7 and 15–21 and letrozole 2.5 mg orally on Days 1–28. For PK testing on Cycle 1 Day 1, patients will take GDC-0032 and letrozole under fasted conditions in the clinic. For subsequent cycles, patients will continue to receive daily

oral doses of GDC-0032 on Days 1–7 and Days 15–21 and daily oral doses of letrozole 2.5 mg orally on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 and letrozole will be administered in the clinic.

- Cohort T: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take oral daily doses of GDC-0032 on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic.

- Cohort T2: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take oral daily doses of GDC-0032 on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic.

- Cohort X, except sub-Cohort X3 patients who are taking GDC-0032 as suspension: In Cycle 1, patients will receive daily oral doses of 4 mg GDC-0032 in tablet form on Days 1–28. For PK testing on Cycle 1 Day 15, patients will take GDC-0032 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take oral daily doses of GDC-0032 on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic.
- Cohort X3: Patients with head and neck cancer who can swallow tablets will receive daily oral doses of 4 mg GDC-0032 in tablet form. For patients who cannot take tablets orally and have gastrostomy (G) tubes, GDC-0032 will be administered via G-tube as an aqueous suspension prepared extemporaneously from GDC-0032 tablets. Patients will be provided with special instructions on how to make a suspension from GDC-0032 tablets. The suspension is prepared by placing the GDC-0032 tablets in water (20 mL of water per tablet) in a glass container for 15 minutes at room temperature. The mixture is then stirred or swirled to generate a suspension before administering into the G-tube. The container should be rinsed with 30 mL of water, and the water from the rinse should also be administered into the G-tube. This rinsing procedure should be repeated one additional time. Suspensions should be prepared immediately prior to dosing. Patients or caregivers should wash their hands after the preparation and any utensils used to prepare the suspension after administration. In Cycle 1, patients will receive daily doses of 4 mg GDC-0032 via G-tube on Days 1–28. Patients or caregivers should prepare GDC-0032 suspension under observation in the clinic on Cycle 1 Days 1 and 2. For PK testing, patients will take GDC-0032 on Cycle 1 Days 1 and 15 under fasted conditions in the clinic. For subsequent cycles, patients will continue to take daily doses of GDC-0032 via G-tube on Days 1–28. For PK testing on Day 1 of Cycles 2 and 6, GDC-0032 will be administered in the clinic. See Appendix B-10 for additional PK testing for Cohort X3 to test the pharmacokinetics of GDC-0032 administered as a suspension.

c. Phase II Dosing

In Cycle 1, patients will receive daily oral doses of GDC-0032 on Days 1–28. Patients will take the GDC-0032 doses on an empty stomach (i.e., 1 hour before or 2 hours after a meal), except on Days 1 and 15 when patients will receive the doses under fasted conditions. Fulvestrant will be supplied in sterile single-patient prefilled syringes containing a 250-mg dose (50 mg/mL fulvestrant as a 5-mL injection). Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1–2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will continue to receive daily oral doses of GDC-0032 on Days 1–28 and will receive fulvestrant as described above in the clinic on Day 1 of each cycle.

For patients with moderate hepatic impairment (Child-Pugh Class B), a single-agent dose of fulvestrant 250 mg is recommended based upon clinical data described in the fulvestrant package insert.

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 and the physician should be notified immediately.

4.3.3 Dose Modification

a. Dose Modifications for Cycle 1 in Stage 1 and Stage 2, Cohorts E and F

Patients who experience a DLT during the DLT assessment window (Days 1–35; see Section 3.1.3) must have GDC-0032 dosing suspended. GDC-0032 will be permanently discontinued, except when the DLT is reversible and monitorable and the risk-benefit ratio suggests a reasonable rationale for the patient to continue in the study, with approval by the Medical Monitor. In such cases, if the DLT resolves to at least the baseline grade within 28 days, GDC-0032 dosing may resume at one dose level lower (as detailed in Table 9). If more than the allowed number of doses of study drugs (see Section 3.1.3 for Stage 1, Section 3.1.4e for Stage 2, Cohort E, and Section 3.1.4f for Stage 2, Cohort F) are missed during this period for reasons other than a DLT, the patient will be replaced in that cohort. Continuation of study treatment for such patients may occur after an assessment of future compliance and discussion between the investigator and the Medical Monitor. No dose reductions are allowed for letrozole (Stage 2, Cohort E) or for fulvestrant (Stage 2, Cohort F).

b. Dose Modifications for Stage 2 Cohorts A–D and G–X, and for Cycles ≥ 2 in Stage 1 and Stage 2, Cohorts E and F

After the DLT assessment window (Stage 1 and Stage 2, Cohorts E and F) and during the continuation phase of the study (Stage 2, Cohorts A–D, and G–X), patients may temporarily suspend GDC-0032 dosing for up to 28 days if they experience a GDC-0032 drug-related toxicity or an unanticipated medical event not associated with study treatment toxicity or with disease progression. Depending on the nature and the severity

of the GDC-0032 related toxicity, patients may resume dosing at the same dose or one dose level lower (as detailed in Table 9 and management guidelines in Section 3.4.5). Initiation and/or increase of anti-hyperglycemic therapy in response to hyperglycemia may be allowed without requiring a dose reduction of GDC-0032, in consultation with the investigator and with the approval of the Medical Monitor.

Table 9 Dose Modifications for GDC-0032 in Stage 2, Cohorts A–D and G–X, and for Cycles 2 and Greater in Stage 1 and Stage 2, Cohorts E and F

GDC-0032	Cohorts A–D and G (Capsules)	Cohorts E and F (Capsules)	Cohort H [b] (Tablets)	Cohorts J and Q [c] (Tablets)	Cohorts K and R [d] (Tablets)	Cohorts L and S [e] (Tablets)	Cohorts M and N (Tablets)	Cohorts P, T, T2, X (Tablets)
Starting dose	9 mg QD	6 mg QD	6 mg QD (21 days on/ 7 days off)	4 mg QD (21 days on/ 7 days off)	4 mg QD (5 days on/ 2 days off)	4 mg QD (7 days on/ 7 days off)	2 mg QD	4 mg QD
First reduction	6 mg QD	3 mg QD	4 mg QD (21 days on/ 7 days off)	2 mg QD (21 days on/ 7 days off)	2 mg QD (5 days on/ 2 days off)	2 mg QD (7 days on/ 7 days off)	2 mg QOD [a]	2 mg QD
Second reduction	3 mg QD	3 mg QOD [a]	2 mg QD (21 days on/ 7 days off)	2 mg QOD [a]	2 mg QD (3 days on/ 4 days off) [a]	2 mg QD (Days 1, 3, 5, 7, 15, 17, 19, and 21) [a]		2 mg QOD [a]
Third reduction	3 mg QOD [a]	—	2 mg QOD [a]	—	—	—		

QD = once daily; QOD = every other day.

[a] If the patient continues to experience specified drug related adverse events after dose reduction, the treatment should be discontinued.

[b] For Cohort H (21 day-on, 7-day off schedule), GDC-0032 will be administered on Days 1–21 of the 28-day cycle. For the third dose reduction, dosing will be converted to 2 mg QOD of the entire 28-day cycle.

[c] For Cohorts J and Q (21-day on, 7-day off schedule), GDC-0032 will be administered on Days 1–21 of the 28-day cycle. For the second dose reduction, dosing will be converted to 2 mg QOD of the entire 28-day cycle.

[d] For Cohorts K and R (5-day on, 2-day off schedule), GDC-0032 will be administered on Days 1–5, 8–12, 15–19, 22–26 of the 28-day cycle. For the second dose reduction, dosing will be 3 days on/4 days off.

[e] For Cohorts L and S (7-day on, 7-day off schedule), GDC-0032 will be administered on Days 1–7 and Days 15–21 of each 28-day cycle. For the second dose reduction, dosing of GDC-0032 will be on the days specified.

Patients may temporarily suspend dosing with letrozole (Stage 2, Cohorts E, N, P, Q, R, and S) or fulvestrant (Stage 2, Cohorts F, J, K, L, and M) for up to 28 days if they experience endocrine therapy-related toxicity or an unanticipated medical event not associated with study treatment toxicity or with disease progression. Letrozole or fulvestrant doses do not necessarily need to be held for GDC-0032-related adverse events. No dose reductions are allowed for letrozole (Stage 2, Cohorts E, N, P, Q, R, and S) or for fulvestrant (Stage 2, Cohorts F, J, K, L, and M). For Stage 2, Cohorts E, F, J, K, L, M, N, P, Q, R, and S, GDC-0032 can be continued if letrozole or fulvestrant has been discontinued.

Patients may suspend dosing for greater than 28 days if the risk-benefit ratio suggests a reasonable rationale for the patient to continue in the study, with approval by the Medical Monitor.

It is not expected that patients in Stage 2, Cohorts A-G receiving capsules will need to switch to tablets. However, in the unlikely event that a patient would need to do so, then the patient would switch to the equivalent expected exposure in tablets (0.67 times the amount in capsules). For example, a patient being treated at the 9-mg capsule dose would switch to a 6-mg tablet dose. A patient at the 6-mg capsule dose would switch to a 4-mg tablet dose. A patient at the 3-mg capsule dose would switch to the 2-mg tablet dose.

c. Dose Modifications for Phase II

Patients may temporarily suspend GDC-0032 dosing for up to 28 days if they experience a GDC-0032-related toxicity or an unanticipated medical event not associated with study treatment toxicity or with disease progression. Patients may suspend dosing for greater than 28 days upon consultation with the Medical Monitor and may resume dosing after a positive risk-benefit assessment for continuing on study. Depending on the nature and the severity of the GDC-0032-related toxicity, patients may resume dosing at the same dose or one dose level lower (as detailed in Table 10 and management guidelines in Section 3.4.5). Initiation and/or increase of anti-hyperglycemic therapy in response to hyperglycemia may be allowed without requiring a dose reduction of GDC-0032.

Table 10 Dose Modifications for Phase II

	GDC-0032 Capsules
Starting dose	6 mg
First reduction	3 mg
Second reduction	3 mg QOD [a]

QOD = every other day.

[a] If the patient continues to experience specified drug-related adverse events after dose reduction, the treatment should be discontinued.

Patients may temporarily suspend dosing with fulvestrant for up to 28 days if they experience endocrine therapy-related toxicity or an unanticipated medical event not associated with study treatment toxicity or with disease progression. Fulvestrant doses do not need to be held for GDC-0032-related adverse events. No dose reductions are allowed for fulvestrant. GDC-0032 can be continued if fulvestrant has been discontinued after investigator assessment of risk/benefit.

Patients may suspend dosing for greater than 28 days if the risk-benefit ratio suggests a reasonable rationale for the patient to continue in the study, with approval by the Medical Monitor.

It is not expected that patients in Phase II currently taking capsules will need to switch to tablets. However, in the unlikely event that a patient would need to do so, then the patient would switch to the equivalent expected exposure in tablets (0.67 times the amount in capsules). A patient at the 6-mg capsule dose would switch to the 4-mg tablet dose. A patient at the 3-mg capsule dose would switch to the 2-mg tablet dose.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations, herbal remedies, and supplements used by a patient from 7 days before screening to the end of study.

Patients who experience toxicities should be treated symptomatically as clinically indicated. Patients treated with anti-seizure medications should have levels monitored regularly.

Patients who use oral contraceptives, hormone-replacement therapy, or other allowed maintenance therapy as specified in the eligibility criteria (see Sections 4.1.2 and 4.1.3) should continue their use. All concomitant medications should be recorded on the appropriate eCRF.

Anti-emetics and antidiarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the investigator, prophylactic anti-emetic and antidiarrheal medication(s) may be used as per standard clinical practice before subsequent doses of study drug.

Pain medications administered per standard clinical practice are acceptable while the patient is enrolled in the study.

4.4.1.1 Infection Prophylaxis

If clinically indicated, anti-infective prophylaxis for viral, fungal, bacterial, or Pneumocystis infections is permitted and should be instituted per institutional practice. Infection prophylaxis for PJP is recommended for patients with NHL enrolled in Cohorts

T and T2 while on treatment and continuing for 2-6 months after discontinuing GDC-0032. The Medical Monitor should be notified if these infections are observed. The potential for drug-drug interactions should be considered (e.g., azoles for fungal prophylaxis).

4.4.2 Excluded Therapy and Foods

Use of the following foods and therapies is prohibited for ≥7 days prior to Day 1 dosing and during the study, unless otherwise specified here or in Section 4.1.3:

- Proton-pump inhibitors (for patients in Stage 2, Cohorts A and C only)
- H2-histamine receptor antagonists within 10 hours prior to and 2 hours after a GDC-0032 dose (for patients in Stage 2, Cohorts A and C only)
- Antacids within 4 hours before a GDC-0032 dose (for patients in Stage 2, Cohorts A and C only)
- Antacid restrictions may be modified for individual patients on the basis of real-time PK data and with agreement by the Medical Monitor.
- Any concomitant therapy intended for the treatment of cancer, whether FDA-approved or experimental, including chemotherapy, radiotherapy, immunotherapy, biologic therapy, herbal therapy, or hormonal therapy (other than letrozole for Stage 2, Cohorts E, N, P, Q, R, and S, and leuprolide for prostate cancer).
- GnRH agonists or antagonists for ovarian suppression
- Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.
- Radiotherapy for unequivocal progressive disease will be as follows: Patients who have demonstrated control of their systemic disease (defined as having received clinical benefit [i.e., a partial response (PR), complete response (CR), or stable disease (SD) for ≥ 3 months]) but who have developed brain metastases that are treatable with radiation will be allowed to continue to receive therapy with GDC-0032 on study until they either experience systemic progression of their disease and/or further progression in the brain (based on investigator assessments). Patients must not miss more than one cycle due to radiation treatment and must have an ECOG performance status of 0, 1, or 2 to continue study treatment. After Cycle 1 (Stage 1; Stage 2, Cohorts E and F) or for all cycles for all other patients, certain forms of radiation therapy may be considered for pain palliation or isolated (e.g., single lesion) progressive disease if patients are deriving benefit, with agreement by the Medical Monitor; study treatment (e.g., GDC-0032, fulvestrant, letrozole) may be suspended during radiation therapy with agreement by the Medical Monitor.
- Quinidine or other anti-arrhythmic agents
- Initiation or increased dose of hematopoietic colony-stimulating factors (e.g., granulocyte colony-stimulating factors [G-CSF; filgrastim], granulocyte/macrophage colony-stimulating factor [GM-CSF; sargramostim], pegfilgrastim, erythropoietin, darbepoetin, and thrombopoietin) from 7 days before

Cycle 1 Day 1 until completion of the DLT Assessment Window in the absence of DLT (Stage 1 and dose-escalation portion of Cohorts E and F in Stage 2).

- After the DLT Assessment window has been completed (or after DLT has been observed), colony-stimulating factors may be administered per standard clinical practice.

Patients who require the use of any of these agents will be discontinued from treatment with GDC-0032 and followed for safety outcomes for 30 days after their last dose of GDC-0032, or until they receive another anti-cancer therapy, whichever occurs first.

Based on in vitro data suggesting that GDC-0032 is metabolized by CYP3A4, the following drugs should be avoided. If use of one of these drugs is necessary, the risks and benefits should be discussed with the medical monitor prior to its concomitant use with GDC-0032:

- Strong/moderate CYP3A4 inhibitors: atazanavir, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, telithromycin, erythromycin, troleandomycin, fluconazole, itraconazole, ketoconazole, voriconazole, posaconazole, aprepitant, conivaptan, fluvoxamine, diltiazem, nefazodone, mibefradil, verapamil, and grapefruit juice or grapefruit supplements
- Strong/moderate CYP3A4 inducers: rifampin, carbamazepine, phenytoin, oxcarbazepine, phenobarbital, efavirenz, nevirapine, etravirine, modafinil, hyperforin (St. Johns Wort), and cyproterone

The investigator will contact the Medical Monitor if questions arise regarding medications not listed above for strong CYP3A4 inhibitors and inducers.

4.5 STUDY ASSESSMENTS

Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient. See Appendices A-1 to A-7 and B-1 to B-14 for the schedule of assessments for the Phase I portion of the study. See Appendices A-8 and B-14 for the schedule of assessments for the Phase II portion of the study. *Patients continuing treatment beyond LPI +6 months will undergo a reduced set of assessments, as outlined in Appendix A-9.*

4.5.1 Definitions of Study Assessments

As of Amendment 10, patients continuing on GDC-0032 beyond LPI +6 months will continue to undergo assessments described in Sections 4.5.1.b, 4.5.1.c, and local assessments described in Section 4.5.1.d. The requirement for assessments described in Sections 4.5.1.e through 4.5.1.v and the central assessments described in Section 4.5.1.d will be removed. All assessments, including those similar to those described in Section 4.5.1.d, may continue as per local standards of care.

a. Medical History and Demographic Data

Medical history includes clinically significant diseases within the last 5 years, surgeries, cancer history (including tumor characteristics), prior cancer therapies and procedures, and all medications used by the patient within 7 days before the screening visit (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies).

Demographic data includes age, sex, and self-reported race/ethnicity.

b. Vital Signs

Vital signs will include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation will be assessed by pulse oximetry after patient has been in a seated position for $\geq$ 5 minutes.

c. Physical Examination

A complete physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

d. Laboratory Assessments

Local laboratory assessment will include the following:

- Hematology: CBC, including RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count
- Fasting ($\geq$ 10-hour fast) serum or plasma chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT
- Fasting glucose
- Fasting insulin (at screening)
- Glycosylated hemoglobin (HbA_{1C})
- Fasting lipid profile: total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, amylase, and lipase
- Coagulation: aPTT (or PTT) and INR
- Serum fibrinogen
- Urinalysis: specific gravity, pH, glucose, protein, ketones, and blood

- Serum or urine pregnancy test: for women of childbearing potential, including premenopausal women who have had a tubal ligation

Instruction manuals and supply kits will be provided for all central laboratory assessments. The following assessments will be performed at a central laboratory or at Genentech:

- Flow cytometry for lymphocyte subsets (CD19, CD3, CD4, CD8, CD16, and CD56) by fluorescence-activated cell sorting (FACS)
- Blood samples for PK analysis (see Section 4.5.1.h and Appendices B-1 to B-14)
- Urine samples for PK analysis (Stage 1 only; see Section 4.5.1.h and Appendix B-1)
- Blood samples for PD analysis (Stage 1 only; see Section 4.5.1.j and Appendix B-1)
- Blood samples for analysis of circulating tumor cells (see Section 4.5.1.k)
- Blood samples for DNA sequencing to identify *PI3K*- and cancer-related mutations in ctDNA (see Section 4.5.1.l)
- Archival tumor tissue sample for evaluation of *PIK3CA* mutation status and other testing (see Section 4.5.1.m)
- Fresh tumor tissue samples for markers (optional [and mandatory in Cohorts N, P, and X3 for select patients]; see Section 4.5.1.n)
- Pharmacogenetic blood sample (see Section 4.5.1.o)
- Blood sample for analysis of cytokines and chemokines (see Section 4.5.1.s)
- For Phase II: On days of study drug administration, predose blood samples for local laboratory assessments should be obtained within 96 hours. All other laboratory samples should be drawn on the day of study drug administration according to the schedule of assessments.

e. Tumor and Response Evaluation

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation (at the end of every even-numbered cycle). Response assessments will be made by the investigator on the basis of physical examinations, imaging studies, laboratory results and bone marrow examinations (if appropriate). For solid tumor cohorts, image-based evaluation using RECIST v1.1 (see Appendix C) will be performed. For Cohort T, the 2007 Revised IWG Response Criteria for Malignant Lymphoma (see Appendix I) will be applied. For Cohort T2, a modified version of the 2014 Lugano Response Criteria for Malignant Lymphoma (see Appendix J) will be applied. Bone scans and brain scans (CT or MRI) will also be performed if clinically indicated. The same radiographic procedure used to define measurable lesions at baseline must be used throughout the study for each patient. Imaging should include CT scans of the chest, abdomen, and pelvis. CT scans of the neck should be included if clinically indicated. At the investigator's discretion, imaging scans may be repeated at any time if progressive disease is suspected. 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.

An assessment of PSA levels will be included for patients who have prostate cancer with non-measurable disease (see Appendix D).

An assessment of CA-125 levels will be included for patients who have ovarian cancer with non-measurable disease (see Appendix E).

An assessment of other tumor markers such as carcinoembryonic antigen (CEA), CA19-9, and α-fetoprotein (AFP) will be included if the marker is elevated at baseline and has been followed in the patient.

Patients with Non-Hodgkin's Lymphoma in Cohort T

Screening and follow-up tumor assessments must include CT scans of the chest, abdomen, and pelvis (with oral/IV contrast unless contraindicated). CT scans of the neck should be included if clinically indicated. If a CT scan of the neck is obtained during screening, then it should continue to be performed throughout the study. CT scans of the brain are not required. FDG-PET, or combined PET-CT, should be performed at screening. If the lymphoma is FDG-avid, FDG-PET, or combined PET-CT, should continue to be performed throughout the study. Response will be assessed by the investigator on the basis of PET and CT scans using the Cheson 2007 criteria (Appendix I). Assessment of B symptoms, LDH, and peripheral blood counts should be performed at screening and with each tumor assessment. Assessment of the bone marrow should include both an evaluation of the bone marrow (i.e., biopsy) for morphology and an aspirate and are required at screening and at the end of Cycle 4, or earlier as per the standard of care. If the bone marrow is involved at screening and still involved at Cycle 4, a subsequent bone marrow examination is required only to confirm a CR. At the investigator's discretion, CT or PET scans may be repeated at any time if progressive disease is suspected.

Patients with DLBCL in Cohort T2

All evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of PET and CT scans, using a modified version of the Lugano 2014 criteria (Appendix J). In this study, the Lugano 2014 criteria for a PET-CT-based CR have been slightly modified to require normal bone marrow for patients with bone marrow involvement at screening. Additionally, designation of PET-CT-based PR requires that CT-based response criteria for a CR or PR be met in addition to the PET-CT-based response criteria for a PR (see Appendix J). Sites will be asked to enter three assessments: Lugano CT response, Lugano PET response, and modified Lugano response.

Additional Response Assessments for Phase II

A technetium bone scan will be performed at screening (up to 28 days prior to Day 1 Cycle 1) to evaluate for the presence of bone metastases. In addition, bone disease identified on bone imaging should be evaluated radiographically by X-ray, CT scan, or MRI. 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 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 the end of 12, 24, and 32 weeks and every 12 weeks thereafter (±7 days for flexibility in the event of isotope shortage) and when clinically indicated. The shorter 8-week interval between Weeks 24 and 32 has been included in order to align the bone scans with other tumor assessments for patient convenience. Any changes in bone imaging should be evaluated radiographically by X-ray, CT scan, or MRI to ascertain the presence of bone destruction versus a healing reaction.

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.

The same imaging modality (bone scan or ^{18}NaF scan) should be used throughout the study. See Appendix H for additional guidance in the event that bone scans are not available because of an isotope shortage. If any shortages in access to technetium are expected, contact the Sponsor or the Imaging Core Facility immediately.

f. QT/QTc and Cardiac Function Evaluations

To assess the impact of GDC-0032 on the QT/QTc interval as well as other ECG parameters, resting digital 12-lead ECGs will be recorded pretreatment (before dosing on Day 1 of Cycle 1) and as detailed in Appendices A-1 through A-8 (triple measurements at each timepoint) in Cycle 1. In Phase I, resting triplicate digital ECGs will also be recorded for safety assessments on Day 1 of Cycles 2–6 and on Day 1 of every even-numbered cycles thereafter, as directed in Appendices A-1 through A-7. In Phase II, resting triplicate digital ECGs will also be recorded for safety assessments as directed in Appendix A-8. Triplicate digital ECG recordings will be obtained within approximately 2–5 minutes of each other at each specified timepoint. The average of the 3 readings will be used to determine ECG intervals (e.g., PR, QT). ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG

resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws.

The triplicate ECGs need to be completed within ± 30 min of the specified PK sample (i.e., PK sample needs to be time-matched to ECG).

If QTc prolongation (>500 msec) is noted, the ECG should be repeated until normalized or stable, underlying causes such as electrolyte imbalances evaluated, an unscheduled PK sample should be obtained (if one was not scheduled at the time of prolongation), and the Medical Monitor should be notified.

g. FDG-PET Imaging

FDG-PET imaging will be required starting with patients enrolled in Cohorts ≥2 in Stage 1 and for all patients enrolled in Stage 2 (Cohorts A–G, L, M, N, Q, R, and S) but will be optional for patients in Cohorts 1 and 2 of Stage 1 (performed only if patients provide specific consent). FDG-PET imaging will not be performed for the Phase II study. If the baseline FDG-PET imaging for a patient shows no detectable tumor FDG uptake, additional FDG-PET imaging will not be required for that patient. Similarly, if there are no significant changes in FDG-PET in Cycle 1, then the FDG-PET imaging in Cycle 2 should not be obtained.

Patients will have the baseline imaging pretreatment (within 14 days prior to dosing on Day 1 of Cycle 1) and will have repeat imaging during the last week of Cycle 1 (e.g., between Days 29–35 for a 35-day cycle), and at the end of Cycle 2 (between Days 22–28). FDG-PET imaging should be performed approximately 1–4 hours after dosing with GDC-0032. Timing and days of FDG-PET imaging may change on the basis of PK and PD data analyzed during the study. FDG-PET imaging may be collected for review by a central facility and by Genentech.

Instructions on preparing patients for FDG-PET are provided in the imaging manual. See Appendix G for additional details on assessments of FDG-PET. See Appendix G for additional details on assessments of FDG-PET imaging.

h. Pharmacokinetic Evaluations

See Appendices B-1 to B-14 for the schedule of PK sample collection. Samples will be collected predose and at various timepoints postdose in Cycle 1. Additional samples will be collected predose at the start of subsequent cycles (Cycles ≥ 2), as detailed in the Appendices B-1 to B-14. The plasma isolated from each blood sample will be split into two aliquots: a primary sample and a back-up sample. Instructions for sample processing and shipping will be provided by a central laboratory.

Urine samples will be collected predose and 0–6 hours and 6–24 hours after dosing on Day 1 in Stage 1 only (see Appendix B-1). Instructions for sample processing and shipping will be provided by a central laboratory.

i. Food–Effect Assessment

This assessment will examine the effects of food on GDC-0032 exposure. A preliminary assessment of the effect of food on GDC-0032 pharmacokinetics will be implemented in Stage 2, Cohort A. Additional PK samples will be collected from patients following GDC-0032 dosing under fasted or fed conditions. See Appendix B-2 for additional details on drug administration and PK sampling for the food effect assessment.

Data from this assessment will be used to guide dosing requirements in subsequent clinical trials with GDC-0032. Details about high-fat meals will be provided in the study reference manual.

j. Surrogate Pharmacodynamics

Blood samples for biomarker evaluation will be collected before the first dose and at several timepoints postdose in Cycle 1 in Stage 1 only and will be processed to obtain platelet-rich plasma for determination of changes in surrogate PD markers (pAKT and possibly others). Instructions for sample processing and shipping will be provided by a central laboratory. See Appendix B-1 for the schedule of blood PD assessments in Stage 1 patients.

k. Blood for Identifying Biomarkers in Circulating Tumor Cells

Blood samples for DNA sequencing to identify PI3K-specific mutations and other cancer-related mutations in CTCs will be collected from all patients (except Cohorts Q, R, S, T, and X) pretreatment, during Cycles 1 and 3, at the study completion visit, and also at the clinic visit subsequent to a confirmed partial or complete tumor response (per RECIST) for any patient as directed in Appendices A-1 through A-8. Instructions for sample processing and shipping will be provided by the central laboratory. See Appendices A-1 to A-8 for the schedule of assessments.

l. Blood for Identifying Cancer-Related Mutations in Circulating Tumor DNA from Plasma

Blood samples for DNA sequencing to identify PI3K-mutations and other cancer-related mutations (e.g., ESR1) in ctDNA will be collected from all patients as directed in Appendices A-1 through A-8. Instructions for sample processing and shipping will be provided by the central laboratory. See Appendices A-1 to A-8 for the schedule of assessments.

m. Evaluation of *PIK3CA* Mutation Status

All potential patients will be asked to provide archival tumor tissue (either paraffin blocks or 15 unstained slides) for mutation testing to occur. For Cohort X (basket study), tissue must be deemed evaluable, as defined in the Laboratory Manual, by central confirmation prior to study enrollment. For Cohort X, if < 10 slides are available, the Medical Monitor must be consulted. For Cohort X, if the patient already has a PIK3CA mutation status report from the Foundation One clinical sequencing assay from Foundation Medicine, the Medical Monitor may be consulted. If archival tissue is not available, patients may

undergo a tumor biopsy for mutational testing to determine eligibility provided the biopsy can be obtained with minimal risk and discomfort to the patient and the patient consents to the procedure. Detailed instructions will be provided in a separate manual.

Screening assessments should be performed after confirmation of *PIK3CA* mutation status for relevant Stage 2 and some Phase II patients. Patients with identified *PIK3CA* mutations will also need to fulfill all other eligibility criteria to enroll in the study.

There are three mutation hotspots in the *PIK3CA* gene: E542K and E545K in exon 9 and H1047R in exon 20; these mutations represent > 80% of all *PIK3CA* mutations described. The frequency of *PIK3CA* mutations in breast cancers has been estimated at 30%-40%. A Taqman qPCR assay or another appropriate assay (e.g., next-generation sequencing [NGS]) will be used for mutation detection. Roche Diagnostics has developed a qPCR assay kit using Taqman technologies to detect mutations in the three hotspots of the *PIK3CA* gene and one rare mutation, E545D, also found in exon 9. Assays from all samples will be run on the Roche Diagnostics cobas 4800 instruments and mutation calls made using the manufacturer's specified protocols. Following histopathologic review, samples with < 20% tumor content will be enriched for tumor content by macro- or micro-dissection. *PIK3CA* testing may be performed at outside facilities to allow the patient to be enrolled, provided that the results are submitted to the sponsor for review before the patient is enrolled; archival tumor tissue will need to be provided for confirmation by central testing.

Additional studies of PI3-kinase–related proteins and PTEN protein expression by IHC may be performed on tissue samples. Additional studies on expression of other PI3K-related proteins may be performed. Other exploratory studies of gene expression, DNA mutations, protein, or DNA markers of PI3K pathway activation may also be conducted on these samples by Genentech or the central laboratory. Tissue blocks from archival biopsies will be returned to the archival facility from which they were originally received.

n. Fresh Tumor Tissue and Other Sample Collection

Optional paired (pre-treatment and post-treatment) tumor biopsy samples for biomarker assessments will be obtained from patients in Phase I (Stages 1 and 2) and Phase II who specifically consent to this procedure. In addition, paired tumor biopsy samples are mandatory for six patient slots (3 patients with *PIK3CA*-wild-type and 3 patients with *PIK3CA*-mutant tumors) in each of Cohorts N and P, and five patient slots in Cohort X3. Patients selected for biopsy should have safe and accessible tumor tissue biopsy sites. Tumor tissue biopsy samples will be obtained prior to starting GDC-0032 treatment. The pretreatment tissue biopsy will be reviewed by a pathologist to determine whether the tissue is evaluable. If the pretreatment tissue is evaluable, a subsequent biopsy will be performed on the day specified below, approximately 1–4 hours after the morning dose. If there is only one lesion for both the biopsy and imaging scans, then the biopsy should be performed either immediately after or ≥ 1 week prior to FDG-PET or other imaging

scans. If two different lesions are being biopsied and scanned, then the second lesion may be biopsied anytime between Days 15 and 21. The timing of the biopsy after dosing may be adjusted on the basis of PK data obtained during the trial. Tumor biopsies upon progression of disease are also optional.

For the following cohorts with a 5-day on 2-day off GDC-0032 dosing schedule, the optional on-treatment biopsy sample should be obtained between Days 15 and 19 of Cycle 1:

- Cohorts K and R

For the following cohorts, the optional or mandatory on-treatment biopsy sample should be obtained between Days 15 and 21 of Cycle 1:

- Cohort H
- Cohorts J, L, M (fulvestrant combination cohorts)
- Cohorts N, P, Q, S (letrozole combination cohorts)
- Cohorts T, T2 (lymphoma)
- Cohort X (Basket)

For Phase II, the optional on-treatment biopsy sample should be obtained between Days 1 and 15 of Cycle 2.

For a patient enrolled in a mandatory paired tumor biopsy slot in Cohort N, P, or X3, if either the pre- or on-treatment biopsy tissue quality is deemed unevaluable by the Central Laboratory, the patient may remain enrolled in the study, but an additional patient may be enrolled to complete the cohort.

In addition, if a patient undergoes a medically indicated procedure any time during the course of the study that has the likelihood of yielding tissue, fluids, or ascites, any remaining samples or a portion of the sample not necessary for medical diagnosis may be obtained for exploratory analysis. Patients must have provided specific consent to obtain optional discarded samples from routine care.

o. Pharmacogenetic Blood Sample

A blood sample will be collected from all eligible patients before initiation of GDC-0032 treatment on Day 1 for potential pharmacogenetic analysis of genes that may affect the pharmacokinetics of GDC-0032 (e.g., drug-metabolizing enzymes and membrane transporters) and genetic variants that could contribute to a potential drug-related adverse event (including but not limited to HLA). Preliminary results from in vitro metabolism studies suggest that GDC-0032 may be a substrate for multiple enzymes and transporters. Genotyping patients for variants in these genes may provide important information about their roles in the metabolism and disposition of GDC-0032. Instructions for sample processing and shipping will be provided. The decision to analyze the samples will be based on a review of the PK and safety data.

p. Effect of GDC-0032 on the Pharmacokinetics of Midazolam (a CYP3A4 Substrate)

This assessment will examine the effects of GDC-0032 on midazolam exposure in Stage 2, Cohort C patients by comparing midazolam plasma exposures (C_{max} and/or AUC_{24hr}) without GDC-0032 (Day 1) and after 15 daily doses of GDC-0032 (Day 16). See Appendix B-4 for additional details on drug administration and PK sampling.

Data from this assessment will be used to guide combination therapies and concomitant medications in subsequent clinical trials with GDC-0032.

q. Assessment of the Pharmacokinetics of GDC-0032 in Combination with Letrozole or Fulvestrant

The pharmacokinetics of GDC-0032 and letrozole or fulvestrant following concomitant administration will be assessed in Stage 2, Cohorts E, N, P, Q, R, and S (letrozole) and F, J, K, L, and M (fulvestrant). The pharmacokinetics of GDC-0032 and fulvestrant will also be assessed in the Phase II portion. Data will be compared to the GDC-0032 PK data collected in this study and historical letrozole or fulvestrant PK data, including plasma exposures, as measured by C_{max} and/or AUC_{24hr}, on Day 15 of Cycle 1. See Appendices B-5, B-6, B-8, B-9, B-12, and B-14 and Figure 5 for additional details on drug administration and PK sampling.

Data from this assessment will be used to guide the design of future GDC-0032 studies in combination with letrozole and/or fulvestrant.

r. Evaluation of *PIK3CA* Copy Number Status

Screening assessments should be performed after confirmation of increased *PIK3CA* copy number for Stage 2, Cohort G patients. Patients with identified amplification of the *PIK3CA* gene will also need to fulfill all other eligibility criteria to enroll in the study. *PIK3CA* amplification testing may be performed at outside facilities provided that the results are submitted to the Sponsor for review before patient enrollment; tumor tissue will need to be provided for confirmation by central testing. Refer to Section 4.8.h for acceptable methodologies.

s. Blood for Analyzing Cytokines and Chemokines from Plasma

Blood samples to assess cytokine and chemokine expression in the plasma will be assessed in Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (as detailed in Appendix A-7). Blood samples will also be collected from patients in the Phase II portion (as detailed in Appendix A-8). Instructions for sample processing and shipping will be provided by the central laboratory.

t. Samples for Optional Exploratory Research

All specimens left over from testing, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides), may be used for exploratory research. The analysis of residual specimens will facilitate the rational design of new pharmaceutical

agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Any leftover samples may be used for exploratory research, provided the patient has specifically consented to this optional research testing. The residual specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

u. Progression Biopsy Collection

Tumor tissue sample may be collected at the time of progression for exploratory research on non-inherited biomarkers and for DNA and/or RNA extraction to enable NGS for exploratory research (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways). Any leftover material will be kept for future research purposes.

NGS may be performed by a clinical cancer genomic profiling laboratory (e.g., Foundation Medicine). If performed by Foundation Medicine, the investigator can obtain results from the samples collected at the time of disease progression in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

v. Cohort T2 DLBCL Tumor Tissue Collection

The following samples will be sent to one or several Sponsor-designated central laboratories or to the Sponsor for analysis: archival or fresh tumor tissue samples and the corresponding pathology report for retrospective central confirmation of the diagnosis of DLBCL, and for exploratory research on candidate biomarkers.

Lymph node resections or biopsies are strongly recommended. The specimen must contain adequate evaluable tumor cells (≥ 20% for excisional biopsy and ≥ 50% for core biopsy). Formalin-fixed paraffin-embedded tissue blocks are preferred over slides. If a tissue block is not available, 15−20 serial, freshly cut, unstained slides accompanied by a punch biopsy may be sent. If fewer than 15−20 unstained serial slides are available, the study site should consult the Sponsor (or delegate) regarding the acceptability of a fewer number of slides.

If archival tissue is unavailable, a pretreatment core-needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

If the available biopsy was performed more than 12 months prior to Day 1 of Cycle 1, or the patient received anti-lymphoma treatment between the time of the most recent available biopsy and Day 1 of Cycle 1, a core-needle biopsy is strongly recommended.

The sample should be shipped according to instructions provided in the laboratory manual. The remainder of the tissue blocks will be returned to the local pathology laboratory, according to country-specific procedures.

Proposed non-inherited biomarkers to be assessed from tumor tissue may include lymphoma-related genetic changes (DNA) and gene expression (mRNA) and protein expression, [PDL-1, HLA-1, CD8, and other biomarkers of T-cell subpopulations, biomarkers of other immune cells (such as macrophages), cytokines, drug transporters, and genes related to regulation of apoptosis].

4.5.2 Screening and Pretreatment Assessments

Screening tests and evaluations will be performed within the 28 days preceding Cycle 1, Day 1 (defined as the day of the first dose of GDC-0032), unless otherwise specified. Results of screening evaluations must be reviewed to confirm that patients meet all eligibility criteria before the first dose of GDC-0032. Written informed consent may be obtained up to 28 days before Cycle 1, Day 1 and before performing any study-specific screening tests or evaluations. Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within the time required for screening may be used for the study rather than repeating these tests. Informed Consent Forms (ICFs) for patients who are not subsequently enrolled will be maintained at the study site.

Pretreatment assessments should be performed only after patient eligibility has been established and informed consents have been signed, and any time prior to the first dose of GDC-0032 at Cycle 1, Day 1 (unless otherwise specified in Section 4.5.1).

See the Study Flowchart provided in Appendices A-1 to A-5, A-7, and A-8 for the schedule of screening and pretreatment assessments.

4.5.3 Assessments during Treatment

All visits must occur within the time windows specified. If a visit is scheduled for a holiday, then dosing may be postponed to the soonest following date with subsequent dosing continuing on a 28-day dosing schedule. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed prior to study drug dosing, unless otherwise noted.

Please see the Study Flowchart provided in Appendices A-1 to A-8 and B-1 to B-14 for the schedule of treatment period assessments. Following the initiation of treatment, patients should be assessed for tumor lysis per local guidelines. *Patients continuing treatment beyond LPI +6 months will undergo a reduced set of assessments, as outlined in Appendix A-9.*

4.5.4 Study Completion/Early Termination Visit

Patients who complete the study (defined as completing 5 years of treatment) or discontinue from the study early will be asked to return to the clinic within 30 days (± 2 weeks) after the last dose of GDC-0032 for a visit. The visit at which the response assessment shows progressive disease may be used as the early termination visit. If a patient discontinues from the study for reasons other than progressive disease (e.g., symptomatic deterioration) and without having a tumor assessment, the patient should have a tumor response assessment at the early termination visit. Patients with unresolved adverse events thought to be related to GDC-0032 must be followed as clinically indicated, until the event is resolved or stabilized, another anti-cancer therapy is initiated, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the adverse event.

The end of the study is defined as the date on which the last patient has their last visit (LPLV).

Please see the Study Flowchart provided in Appendices A-6 *to A-9* for assessments to be performed at the study completion/early termination visit.

4.5.5 Follow-Up Assessments

Patients with unresolved adverse events thought to be related to GDC-0032 must be followed as clinically indicated, until the event is resolved or stabilized, another anti-cancer therapy is initiated, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the adverse event.

For patients enrolled in Phase I, Stage 2, Cohorts H–X and the Phase II portion of the study, survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by Genentech. All patients will be followed for survival information unless the patient requests to be withdrawn from study survival follow-up. The request must be documented in the source file and signed by the investigator. If the patient withdraws from the study treatment but not from study follow-up, the study staff may use a public information source (such as county records) to obtain information about survival status only.

4.6 PATIENT DISCONTINUATION

Patients may withdraw or be withdrawn from the study at any time. Any patient who discontinues treatment should be encouraged to return to the study site for a treatment

completion/early termination evaluation (see Section 4.5.4). The primary reason for discontinuation must be recorded on the appropriate eCRF.

Patients must be withdrawn from study treatment if they experience any of the following:

- Disease progression (defined using RECIST v 1.1; see Appendix C)
- In Cohort T: Disease progression (defined using the 2007 IWG Revised Response Criteria for Malignant Lymphoma; see Appendix I)
- In Cohort T2: Disease progression (defined using the 2014 Lugano Response Criteria for Malignant Lymphoma; see Appendix J)
- Use of another anti-cancer therapy (see Section 4.4)

Other reasons for patient discontinuation may include, but are not limited to, the following:

- In general, patients experiencing a DLT (see Section 3.1.3.a for DLT definition) during the DLT assessment window should discontinue from the study. However, under certain circumstances where the adverse event is reversible, monitorable, and the risk/benefit suggests a reasonable rationale to continue on the study, patients may continue with consultation with the medical monitor.
- Excessive pill burden, defined as 2 or more patients in a cohort who are unable to take $\geq$90% of their doses at a dose level that requires a minimum of seven capsules or tablets to be taken per dose
- Change in patient eligibility
- Non-compliance with protocol-specified study visits and procedures
- Investigator decision based on the patient's best interest
- Patient decision

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study and for reasons of noncompliance (e.g., missed doses, visits) or pregnancy or if the investigator determines it is in the best interest of the patient.

See Section 4.5.4 and Appendix A-6, A-7, and A-8 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

Treatment Post-Progression

Under special circumstances, when it is believed that the patient may clinically benefit from continued therapy with GDC-0032, dosing beyond progression may be considered if it is judged by the investigator, in consultation with the Sponsor, to be in the best interest of the patient. Only patients who have experienced some clinical benefit as assessed by the investigator will be eligible for continued treatment. Considered patients must remain "on study" and cannot have initiated any other anti-cancer therapy.

All such cases will require approval of the Sponsor before continuing study drug treatment within this protocol.

STUDY DISCONTINUATION

Genentech 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.
- Data recording is inaccurate or incomplete.

Genentech will notify the investigator if Genentech decides to discontinue the study.

Genentech 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 ICH guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

4.7 POST-TRIAL ACCESS

Genentech does not intend to provide GDC-0032 or other study interventions to patients after the conclusion of the study or any earlier withdrawal. Genentech will evaluate whether to continue providing GDC-0032 in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

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

4.8 ASSAY METHODS

a. Mutational Analysis for PIK3CA

Mutations in the *PIK3CA* gene have been estimated at a prevalence of 30%–40% in breast cancers. A Taqman quantitative PCR (qPCR) assay or another appropriate assay, such as NGS, will be used for mutation detection. Roche Diagnostics has developed a qPCR assay kit to detect mutations in common hotspots of the *PIK3CA* gene. Samples may be run on the Roche Diagnostics cobas 4800 instruments and mutation calls using appropriate cutoffs and automated software. Following histopathologic review, samples with $<$20% tumor content will be enriched for tumor content by macro- or micro-dissection. Somatic mutations in the *PIK3CA* gene are found in approximately 30% of breast cancers and occur most commonly in exons 9

and 20 in the codons encoding amino acids E542, E545, and H1047. Real time PCR assays that amplify exons 9 and 20 of *PIK3CA* offer a sensitive and quantitative method to detect mutations from archival tumor material. DNA will be extracted from tumor samples and subjected to quantitative real-time PCR (qRT-PCR) assays that detect the wild-type allele, as well as assays for nucleotide substitutions that include but are not limited to the following amino acid changes: E542 (K), E545 (A, G, or K), and H1047 (L, R, Y). Assays from samples will be run on ABI7900 Real Time PCR instruments and mutation calls made using appropriate cutoffs and automated software.

b. PTEN Testing

PTEN status will be examined by immunohistochemistry using a protocol that has been validated for specificity using several available cell line controls. Archival tumor material will be scored only if appropriate staining is observed in internal control stromal or normal (non-tumor) tissue elements. PTEN status may also be examined by qRT-PCR assay for mRNA levels, by use of NGS platform or chromosomal loss by use of in situ hybridization techniques (e.g., FISH or chromogenic in situ hybridization [CISH]).

c. Circulating Tumor Cell and Circulating Tumor DNA Analyses

CTC analysis will be performed on whole blood using the Cellsearch, Biocept, Cellective and/or other CTC enumeration and molecular profiling platforms. In addition, ctDNA will be extracted from plasma samples collected from patients and used for the detection of oncogenic mutations using appropriate technologies. The prevalence of the mutations measured at baseline and post-treatment may provide information on response or resistance to therapy.

d. mRNA and miRNA Expression Profiling

In cases where there is sufficient archival tissue to isolate RNA, gene expression of a panel of genes and microRNAs including, but not limited to, cancer biology and/or PI3K signaling, will be performed using qRT-PCR assays conducted on the Fluidigm Biomark or equivalent platform, such as NanoString, or by use of NGS platforms (RNAseq). The goal will be to generate a database of expression status to examine whether there are gene expression patterns that are associated with clinical response to GDC-0032.

e. Plasma and Urine PK Samples

Plasma PK samples for GDC-0032 will be analyzed using a validated LC/MS/MS method and the urine PK samples will be analyzed using a separate non-validated LC/MS/MS method at a Genentech-designated laboratory. After the plasma and urine samples are analyzed, any remaining samples may be used for optional exploratory research.

f. Blood PD Assays

Blood samples for PD measurement will be separated to yield the platelet-rich plasma (PRP) and the platelet-poor plasma (PPP). Pathway biomarkers, such as pAKT S473, will be measured in PRP by modified MSD (Meso Scale Discovery, Gaithersburg,

Maryland) based-assays. Circulating angiogenesis factors will be measured by immunoassays in PPP.

g. PD Biomarker Assays in Tumor Tissues

PI3-kinase pathway biomarkers will be tested in the fresh tumor biopsy samples by IHC and, if tissue quantity permits, change in expression or phosphorylation status of additional pathway biomarkers will be measured by the reverse phase protein array (RPPA), or other technologies. The basis of the technology is to immobilize small amounts of lysate from a tumor biopsy sample in serial dilution on a microarray slide. Multiple samples are thus arrayed on a slide and can be probed with antibodies that detect a particular phospho-epitope. Using this technology, we will profile ~100 key signaling nodes representing a number of pathways known to be dysregulated in cancer, including receptors in the HER family, multiple components of PI3K/mTor signaling, as well as key members of the RAS/MAP kinase pathway.

h. Copy Number Analysis of PIK3CA Gene

The level of amplification of the *PIK3CA* gene should be determined using DNA based technologies, either cytogenetically using chromosomal ISH with labeled probes spanning the *PIK3CA* locus or using NGS platforms. For cytogenetic assays, detection may be either fluorescence-based (FISH assay) or CISH-based detection. Chromosomal ploidy changes that involve the entire chromosome may be assessed by ISH for a chromosome 3 centromeric probe (CEP3). Refer to the laboratory manual for definition of *PIK3CA* amplification.

i. Chemokine and Cytokine Analyses

Assays to assess the expression of soluble, systemic cytokines and chemokines from the plasma of patients will be carried out using an ELISA-based or similar methodology.

j. *KRAS* Mutation Testing

KRAS-mutation testing applies only to patients enrolled in the *KRAS* wild-type colorectal cancer Basket-Cohort X8. *KRAS* mutations may be tested at a Genentech-designated Central Reference Laboratory or per institutional guidelines. If a non–Genentech-designated laboratory is used for *KRAS*-mutation testing, documentation of the test procedures and results must be included as source documentation. *KRAS*-mutation testing may be performed with the Qiagen Therascreen KRAS RGQ PCR-based assay or other appropriate technologies. Only patients whose tumors test negative for a *KRAS* mutation (i.e., *KRAS* wild-type) will be eligible for enrollment in this study cohort, if other eligibility criteria are met. Tumor samples may be obtained from the primary cancer or any metastatic site.

k. Next-Generation Sequencing

NGS provides a powerful approach to determine the alterations of somatic mutations in key cancer genes with broad mutation coverage. Panels have been developed to

characterize the most frequently mutated oncogenes and tumor suppressors in various cancer types.

4.9 STATISTICAL METHODS

The final analysis will be based on patient data collected through patient discontinuation or study discontinuation, whichever occurs first. All analyses will be based on the safety-evaluable population, defined as all patients who receive at least one dose of GDC-0032, letrozole, or fulvestrant. All summaries will be presented according to the assigned dose level and cohort.

4.9.1 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and reasons for discontinuations from the study will be summarized by dose level and cohort.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, type of malignancy, duration of malignancy, site of metastatic disease, and baseline ECOG performance status, will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables.
All summaries will be presented overall and by assigned dose level.

4.9.2 Safety Analyses

Safety will be assessed through summaries of adverse events, changes in laboratory test results, and changes in vital signs. All patients who receive any amount of GDC-0032 will be included in the safety analyses.

GDC-0032 exposure, including the proportion of patients with dose modifications, will be summarized by assigned dose level and cohort.

All collected adverse event data will be listed by study site, patient number, and cycle. All adverse events occurring on or after treatment on Day 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade.
In addition, all serious adverse events, including deaths will be listed separately and summarized.

QT/QTc data will be analyzed using the E14 guidelines and may include analyses of central tendency, categorical analyses, analysis of the relationship between drug exposure and QT/QTc interval changes, and morphologic analyses of ECG waveforms.

4.9.3 Pharmacokinetic Analyses

Individual plasma GDC-0032 concentration vs. time data and summary statistics will be tabulated by dose level and schedule. Individual and mean (SD) plasma concentration versus time profiles will be plotted.

The plasma GDC-0032 pharmacokinetic data obtained after a single dose (Day 1) and at steady state (Day 15) will be analyzed using noncompartmental methods to estimate PK parameters, which include but are not limited to $AUC_{0-\tau}$ and/or AUC_{0-inf}, C_{max}, C_{min}, t_{max}, $t_{1/2}$, CL/F, accumulation (AR), renal excretion fraction (fe), urinary CL (CLr). Additional PK parameters may be determined as data allow. Estimates for these parameters and summary statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum) will be tabulated by dose level and schedule.

For Phase II, GDC-0032 and fulvestrant plasma concentrations will be tabulated from individual patients and presented with appropriate summary statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

4.9.4 Food-Effect Analyses

For patients participating in the food–effect assessment in Stage 2, Cohort A, the effects of food versus fasting states on C_{max}, t_{max}, and AUC_{0-24} of GDC-0032 will be examined based on intra-subject comparison. Estimates of these parameters and summary statistics will be tabulated. The food effect on the pharmacokinetics of GDC-0032 will be estimated as the ratio of geometric mean values of C_{max} and AUC_{0-24}, and the corresponding 90% confidence intervals (CIs) will be constructed.

4.9.5 Analyses of Effect of GDC-0032 on the Pharmacokinetics of Midazolam

For patients participating in Stage 2, Cohort C, the effects of GDC-0032 on C_{max}, t_{max}, and AUC_{0-24} of midazolam will be examined based on intra-subject comparison. Estimates of these parameters and summary statistics will be tabulated. The effect of GDC-0032 on the pharmacokinetics of midazolam will be estimated as the ratio of geometric mean values of C_{max} and AUC_{0-24} and the corresponding 90% CIs will be constructed.

4.9.6 Analyses of the Pharmacokinetics of GDC-0032 in Combination with Letrozole

For patients participating in Stage 2, Cohorts E, N, P, Q, R, and S the pharmacokinetics of GDC-0032 and letrozole, as measured by C_{max}, t_{max}, and AUC_{0-24}, will be estimated and the summary statistics will be tabulated.

4.9.7 Analyses of the Pharmacokinetics of GDC-0032 in Combination with Fulvestrant

For patients participating in Stage 2, Cohorts F, J, K, L, and M, and Phase II, the pharmacokinetics of GDC-0032 and fulvestrant, as measured by C_{max}, t_{max}, and AUC_{0-24}, will be estimated and the summary statistics will be tabulated.

4.9.8 Activity Analyses

a. Tumor Assessment Data

Objective overall response will be summarized for safety-evaluable patients with baseline measurable disease by dose level and schedule. Duration of response and PFS will be summarized for all safety evaluable patients by dose level and schedule.

Objective overall response in patients with measurable disease is defined as a complete or partial response, as determined by investigator assessment using RECIST v1.1 (see Appendix C) and confirmed by one consecutive assessment ≥4 weeks after initial documentation. Response for lymphoma patients (Cohort T) will be assessed using the 2007 IWG Revised Response Criteria for Malignant Lymphoma (Appendix I). Response for DLBCL patients (Cohort T2) will be assessed using a modified version of the 2014 Lugano Response Criteria for Malignant Lymphoma (Appendix J). Patients with measurable disease at baseline who do not meet this criterion will be considered non-responders.

In patients with disease that is evaluable but not measurable by RECIST v1.1, response will be assessed either quantitatively, in the case of patients with elevated tumor markers (PSA or CA-125; see Appendices D and E), or descriptively (e.g., resolution of bone scan findings, decrease in tumor-related pain symptoms). Any patient with insufficient data to determine response will be classified as a non-responder.

Among patients with an objective overall response, duration of response will be defined as the time from the initial complete or partial response to the time of disease progression or death, whichever occurs first. If a patient has not experienced disease progression or death, duration of response will be censored at the day of the last tumor assessment showing no disease progression.

PFS will be defined as the time from the first day of GDC-0032, fulvestrant, or letrozole treatment until documented disease progression, or death on study (defined as death within 30 days of last study drug administration), whichever occurs first. For patients who do not have documented progressive disease or death on study, PFS will be censored at the day of the last tumor assessment showing no disease progression. If a patient has no post-baseline tumor assessment, PFS will be censored at the day of the first dose of study drug administration. PFS will be summarized using the Kaplan-Meier method.

The 6-month clinical benefit will be defined as a confirmed complete response, confirmed partial response, or without disease progression for ≥ 6 months per RECIST v1.1.

Among patients with clinical benefit, duration of clinical benefit will be defined as the time from the first day of GDC-0032 treatment until documented disease progression, or death on study, whichever occurs first. If a patient has not experienced disease

progression or death, duration of clinical response will be censored at the day of the last tumor assessment showing no disease progression.

Analysis methods for the expansion cohorts will include a summary of adverse events, an estimation of objective overall response rate (ORR) and its corresponding 95% Pearson-Clopper exact confidence interval.

4.9.9 Exploratory Analyses

a. Pharmacodynamic Analyses

PD analyses will include imaging studies and assessments of PD biomarkers in both tumor tissue and blood.

The effect of GDC-0032 on FDG-PET will be assessed on the basis of the maximum standardized uptake value (SUV_{max}) of up to five tumor regions of interest (ROIs). The tumor ROIs will be identified for each patient from pretreatment imaging. Determination of PET response will be based on the modified definitions of the European Organisation for Research on the Treatment of Cancer (EORTC; Young et al. 1999). The percent change in the SUV_{max} will be quantified. In the event of more than one ROI, the overall percent change in SUV_{max} will be based on the arithmetic mean ($mSUV_{max}$). The selected ROIs should overlap with RECIST target or non-target lesions identified at baseline and have FDG uptake. FDG-PET response rates will be calculated and, where sample sizes warrant, exact 95% confidence intervals for the above response rates will be presented using the Pearson-Clopper method. FDG-PET imaging will be independently read and analyzed by a central reviewer and by Genentech for SUV changes. Other parameters, such as SUV_{mean}, may also be analyzed. Given the exploratory nature of these analyses, results of FDG-PET imaging will not be used to determine disease status during treatment with GDC-0032.

The PD effect of GDC-0032 in blood cells will be assessed through changes from baseline in pAKT levels and other pathway biomarker levels in platelet-rich plasma in Stage 1. The relationship of GDC-0032 exposure with magnitude of effect on pAKT and other biomarker levels may be described.

Tumor biopsy samples will be tested for the expression of multiple phospho-proteins in cell signaling pathways, including the PI3K pathway. Inhibition of the PI3K pathway is defined as $>60\%$ inhibition of two or more phospho-proteins in the same pathway compared to baseline in a particular patient. The percentage of patients with significant PI3K pathway inhibition will be assessed. The degree of inhibition of various pathway markers in each patient and their relationship to PK, safety, and tumor response will be explored.

Changes in PD biomarkers will be listed by dose, cohort, and response status. Additional PK and PD analyses will be conducted as appropriate.

b. Expression and Mutational Analyses on Cancer-Related Proteins and Genes

Association of PD and anti-tumor activity and *PI3K* mutation status, *PI3K* amplification, degree of loss of PTEN expression, and/or other cancer-related mutations in archival tissue and fresh tumor tissue (for patients who elect to provide biopsy samples) may be analyzed. Mutations in ctDNA and CTCs may also be assessed.

c. Pharmacogenomic Analysis

In the event that PK analyses become difficult to interpret, gene mutations may be assayed using multiplex PCR, allele-specific PCR, direct sequencing, or other appropriate method. PK parameters, including dose-normalized AUC and C_{max}, would be compared between genotypes and, where possible, predicted phenotypes.

4.9.10 Determination of Sample Size

A total of approximately 623–723 patients are expected to be enrolled in this study. In the single-agent dose-escalation portion of this study (Stage 1 of Phase I), 34 patients have been enrolled. Approximately 529–629 patients are expected to be enrolled in Stage 2 of Phase I, including with Amendment 8, 6 additional patients each in Cohorts N and P; 20 patients each in Cohorts Q, R, and S; 10 lymphoma patients in Cohort T; 10–20 DLBCL patients in Cohort T2; 10–20 patients in each sub-cohort of the basket Cohort X (X1-X10); 20–40 patients in sub-Cohort X3; and 50 patients in sub-Cohort X11 with *PIK3CA*-mutant tumor types not covered in X1-X10. Phase II has fully enrolled with a total of 60 patients.

a. Stage 1: Dose Escalation

The sample size for Stage 1 is based on the dose-escalation rules described in the study design section of this protocol (see Section 3.1.3). The sample size for this trial is not based on explicit power or type I error considerations.

Table 11 describes the probabilities of dose escalation with different underlying rates of DLT and the performance of 3+3 dose-escalation schemas when certain assumptions hold for the study drug. As GDC-0032 has not been studied in humans before, it is not known whether these assumptions hold for this study.

Table 11 Probability for the Dose-Escalation Rules with Different Underlying Rates of Dose-Limiting Toxicity

Underlying Rate of Dose-Limiting Toxicity	Probability That Dose Escalation Proceeds
0.10	0.91
0.20	0.71
0.33	0.43
0.40	0.31
0.50	0.17
0.60	0.08

The following assumptions were made to generate Table 11:

- The observed number of patients experiencing a DLT follows a binomial distribution.
- Given a true rate of DLT, the probability of observing a DLT is the same for each patient.
- The probability that dose escalation proceeds is the probability of observing either of the following in the current dose cohort: (a) none of the first 3 patients in the cohort experiences a DLT, or (b) 1 of the first 3 patients in the cohort experiences a DLT, the cohort is expanded to include another 3 patients, and none of the additional patients experiences a DLT.

The final sample size for Stage 1 of this trial will be determined by the dose-escalation rules described in Section 3.1.3.

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in a given cohort of 6 patients is 46.9%, 26.5%, and 5.8%, respectively.

b. Stage 2: Expansion Cohorts

To better characterize the safety of single-agent GDC-0032 administered at the recommended dose for future studies, approximately 82 patients will be enrolled and treated with single-agent GDC-0032 in Stage 2, Cohorts A–D and G. For a given adverse event with a true rate of 10%, 5%, or 1% the probability of observing at least one such adverse event in 82 patients from the single-agent GDC-0032 expansion cohorts (Stage 2, Cohorts A–D and G) is $>$99.9%, 98.5%, and 56.1%, respectively.

Cohorts A–D and G–H of Stage 2 encompass distinct patient populations that may have differing safety profiles. For example, Cohort D includes HER2-positive metastatic breast cancer patients, whereas Cohort G includes patients with solid tumors that have increased *PIK3CA* copy number.

Increasing the size of Cohorts A and B to 20 patients will provide more robust safety data in the patient populations tested. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in 20 patients is 87.8%, 64.1%, and 18.2%, respectively. Cohort H will also provide more robust safety data on a different single-agent schedule of GDC-0032 being given on a 21-day on, 7-day off (21/7) schedule. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in an expanded cohort of 40 patients is 98.6%, 87.1%, and 33.1%, respectively.

To better characterize the safety of the combination of GDC-0032 with either letrozole (Stage 2, Cohort E) or with fulvestrant (Stage 2, Cohort F), approximately 27–28 patients will be enrolled in each of these expansion cohorts. This number includes the possibility that two dose levels will be tested as described in Sections 3.1.4.e and 3.1.4.f with 20 patients enrolled at the selected dose level.

Promising anti-tumor activity has been observed at the 6-mg QD capsule dose level of GDC-0032 in combination with letrozole (Cohort E) and in combination with fulvestrant (Cohort F). Several alternate dose schedules will be evaluated to obtain additional data on the relative tolerability of adding intermittent breaks to the GDC-0032 dosing schedule or lower doses of GDC-0032 in combination with either fulvestrant (Cohorts J, K, L, M) or letrozole (Cohorts N, P, Q, R, and S).

Approximately 20 patients will be enrolled into Stage 2, Cohort J to evaluate an alternative dose schedule of GDC-0032 4-mg QD tablet dose level with a 21-day on, 7-day off (21/7) schedule in combination with fulvestrant.

Approximately 20 patients will be enrolled into Stage 2, Cohort K to evaluate an alternative dose schedule of GDC-0032 4-mg QD tablet dose level with a 5-day on, 2-day off (5/2) schedule in combination with fulvestrant.

Approximately 20 patients will be enrolled into Stage 2, Cohort L to evaluate an alternative dose schedule of GDC-0032 4-mg QD tablet dose level with a 7-day on, 7-day off (7/7) schedule in combination with fulvestrant.

Approximately 20 patients will be enrolled into Stage 2, Cohort M to evaluate an alternative dose level of GDC-0032 2-mg QD tablet dose level in combination with fulvestrant.

Approximately 26 patients will be enrolled into Stage 2, Cohort N to evaluate an alternative dose level of GDC-0032 2-mg QD tablet dose level in combination with letrozole. This includes six patient slots (three with *PIK3CA*-mutant and three with *PIK3CA*-wild-type tumors) in which paired pre- and on-treatment tumor biopsies are required.

Approximately 26 patients will be enrolled into Stage 2, Cohort P to evaluate an alternative dose level of GDC-0032 4-mg QD tablet dose level in combination with letrozole in a less heavily pretreated population as compared with Stage 2, Cohort E. This includes six patient slots (three with *PIK3CA*-mutant and three with *PIK3CA*-wild-type tumors) in which paired pre- and on-treatment tumor biopsies are required.

For the 12 slots in Cohorts N and P in which paired pre- and on-treatment tumor biopsies are required, if a patient enrolls in the study and either the pre- or the on-treatment biopsy tissue quality is deemed unevaluable by the Central Laboratory, the patient may continue on treatment, but additional patients may be enrolled to complete the cohort (at the Sponsor's discretion). The paired tumor biopsies support the exploratory objective of assessing GDC-0032 PD effects on the PI3K (and other) pathways. Therefore, a limited number of patients (3 patients with *PIK3CA*-mutant and 3 patients with *PIK3CA*-wild type tumors in each cohort) was chosen to provide a preliminary PD assessment.

Approximately 20 patients will be enrolled into Stage 2, Cohort Q to evaluate an alternative dose schedule of GDC-0032 4-mg tablet dose level with a 21-day on, 7-day off (21/7) schedule in combination with letrozole.

Approximately 20 patients will be enrolled into Stage 2, Cohort R to evaluate an alternative dose schedule of GDC-0032 4-mg QD tablet dose level with a 5-day on, 2-day off (5/2) schedule in combination with letrozole.

Approximately 20 patients will be enrolled into Stage 2, Cohort S to evaluate an alternative dose schedule of GDC-0032 4 mg QD tablet dose level with a 7-day on, 7-day off (7/7) schedule in combination with letrozole.

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in an expanded cohort of 20 patients is 87.8%, 64.1%, and 18.2%, respectively. This is especially important in characterizing an adverse event such as pneumonitis that may occur at a low frequency. It is important to understand the safety profile of GDC-0032 in combination with letrozole as this regimen may be tested in future studies for patients with early hormone receptor–positive breast cancer, an indication with a unique risk-benefit profile. The combination of GDC-0032 and fulvestrant may be tested in future studies as an early-line therapy for patients with advanced hormone receptor–positive breast cancer.

In Cohort T, to characterize the safety and tolerability of single-agent GDC-0032 for patients with lymphoma, approximately 10 patients will be enrolled, irrespective of their tumor's *PIK3CA*-mutation status. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in an expanded cohort of 10 patients is 65.1%, 40.1%, and 9.6%, respectively.

In Cohort T2, to characterize the safety and tolerability of single-agent GDC-0032 for patients with DLBCL, approximately 10–20 patients will be enrolled, irrespective of their tumor's PIK3CA-mutation status. If less than 2 responders (CR or PR, confirmed or unconfirmed) are observed from the first 10 patients with DLBCL, enrollment will be suspended for Cohort T2; if 2 or more responders are observed from the first 10 patients, another 10 patients may be enrolled into the cohort. However, if clinical benefit is observed for the first 10 patients with DLBCL in Cohort T2 (e.g., a majority of patients demonstrate SD at Week 8 although there are less than 2 responders), then further enrollment of 10 additional patients may be allowed for this cohort, depending on the decision made by the Sponsor. Assessment for expansion of Cohort T2 will be made on a rolling basis, depending on when responses are observed. In addition, a decision about further enrollment of additional patients beyond 20 will be made by the Sponsor if clinical benefit is observed (e.g., $\geq$ 4 PR in 20 patients).

In Cohort X (sub-Cohorts X1–X10), to provide preliminary efficacy and safety data of single agent GDC-0032 in a diverse population of patients with *PIK3CA*-mutant cancer, the following rule will be applied to each of the sub-cohorts: if less than 2 responders (CR or PR, confirmed or unconfirmed) are observed from the first 10 patients with *PIK3CA*-mutant cancer, enrollment will be suspended for that indication; if 2 or more responders are observed from the first 10 patients, another 10 patients will be enrolled into the cohort. However, if clinical benefit is observed for the first 10 patients with *PIK3CA*-mutant cancer in the cohort (e.g., a majority of patients demonstrate SD at Week 8 although there are less than 2 responders), then further enrollment of 10 additional patients may be allowed for this cohort, depending on the decision made by Genentech. Assessment for expansion of a given sub-cohort will be made on a rolling basis, depending on when responses are observed. These expansion rules will also be applied for the 10-20 patients with HNSCC with amplification of the PIK3CA gene number and no PIK3CA somatic mutations detected in Cohort X3. In addition, if a given indication is expanded to 20, a decision about further enrollment of additional patients beyond 20 (up to a maximum of 40 for any given indication, e.g., PIK3CA-mutant HNSCC) will be made by the Sponsor if clinical benefit is observed (e.g., $\geq$ 4 PR in 20 patients).

A positive *PIK3CA*-mutation or amplification status from local testing will be centrally confirmed for patients in Cohort X. If a patient enrolls as per a positive local test result and a mutation or amplification is not detected per central testing, the patient will be allowed to continue in the study, and additional patients may be enrolled to meet enrollment goals of patients with *PIK3CA*-mutant or amplified tumors.

With the assumption of an expected true response rate of 30% or higher, there is at most a 15% chance of observing less than 2 responses in 10 patients, which is the false negative rate. If the true response rate increases to 40%, the false negative rate decreases to 5%. Alternately, with the assumption of a response rate of 5% or less, there is at most a 9% chance of observing 2 or more responses in 10 patients, which is

the false positive rate. If the response rate decreases to 4%, the false positive rate decreases to 6%.

Assuming a preferable response rate was observed (≥ 20% responders) at Week 8 in Cohort T2 and X and 10 additional patients were enrolled, with an observed response rate of 20%, a sample size of 20 patients within a given indication (i.e., sub-Cohorts X1–X10) would result in an 80% Pearson-Clopper exact CI of 9% to 36%, excluding a response rate of 8%. Assuming that the observed responder rate is 20% with 20 patients in a sub-cohort of Cohort X, and that an additional 20 patients were enrolled, the resulting sample size of 40 patients within a given indication would result in an 80% Pearson-Clopper exact CI of 12% to 30%, which is narrower than when the sample size is 20, thus providing more confidence in the observed response rate. The precision of the estimation under different observed response rates is illustrated in Table 12, through 80% Pearson-Clopper exact CIs.

Table 12 Confidence Intervals under Different Response Rates

80% Pearson-Clopper Exact CIs (%)	Sample Size				
Response Rate (%)	10	20	30	40	50
5	0–27	1–18	1–15	1–13	2–12
10	1–34	3–24	4–21	4–19	5–18
15	3–39	6–30	7–27	8–25	9–24
20	5–45	9–36	11–32	12–30	13–29
25	8–50	13–41	15–38	16–36	17–35
30	12–55	17–47	19–43	20–41	21–40

CI = confidence interval.

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in an expanded cohort of 20 patients is 87.8%, 64.2%, and 18.2%, respectively; in an expanded cohort of 40 patients the probability is 98.5%, 87.1%, and 33.1%, respectively. Table 13 describes the 80% Pearson-Clopper CI under different AE rates with 10-50 patients.

Table 13 Confidence Intervals under Different Underlying Adverse Event Rates

80% Pearson-Clopper Exact CIs (%)	Sample Size				
Underlying Adverse Event Rate (%)	10	20	30	40	50
1	0–22	0–12	0–9	0–7	0–6
5	0–27	1–18	1–15	1–13	2–12
10	1–34	3–24	4–21	4–19	5–18

CI = confidence interval.

In sub-Cohort X11, approximately 50 patients will be enrolled with *PIK3CA*-mutant tumors not otherwise specified in sub-Cohorts X1–X10 and excluding breast cancer, NSCLC, and colorectal cancer. With 50 patients, the probability of observing at least one such adverse event with a true rate of 10%, 5%, or 1% will be 99.5%, 92.3%, and 39.5%, respectively.

c. Phase II

The Phase II portion of the trial will evaluate safety and provide a preliminary evaluation of efficacy of the combination of GDC-0032 and fulvestrant as measured by ORR and CBR. The study is designed to estimate the ORR and the CBR with reasonable precision to contrast the results of this study with historical data from studies with fulvestrant in a similar patient population, which have ORR of 7%–10% and CBR rate of 32%–46% (Chia et al. 2008; Di Leo et al. 2010). CBR allows for evaluation of bone-only disease patients while ORR does not. Based upon previous literature, bone-only disease is approximately 30% of patients (Chia et al. 2008; Di Leo et al. 2010).

The Phase II portion of this trial will be able to detect a large benefit of the combination of GDC-0032 and fulvestrant, in terms of ORR. For example, an observed ORR of ≥ 30% in 21 patients with *PIK3CA* mutant tumors (assuming 30% of the 30 patients will have non-measurable bone only disease) will have a 95% confidence interval of (14.6%, 57.0%), excluding an ORR of 10%. Similarly, an observed CBR of 67% in 30 patients will have a 95% confidence interval of (47.2%, 82.7%), excluding a CBR of 46%.

4.10 DATA QUALITY ASSURANCE

The data will be collected via Electronic Data Capture (EDC) using eCRFs. The site 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 CRO will be responsible for the data management of this trial, including quality checking of the data.

Genentech will perform oversight of the data management of this trial. Genentech will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central Laboratory data and other electronic data will be sent directly to Genentech, using Genentech'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 at Genentech and records retention for the study data will be consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

Genentech or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Genentech or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Genentech or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

5.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with cancer that were not present prior to the AE reporting period (see Section 5.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)

- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g. invasive procedures such as biopsies, medication washout, or no treatment run-in).
- Preexisting medical conditions (other than cancer), judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

5.1.2 Serious Adverse Events

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the investigator (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

Serious adverse events are required to be reported by the investigator to Genentech immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.1.3 Protocol-Defined Events of Special Interest/Non-Serious Expedited Adverse Events

The following events are events of special interest and will need to be reported to the Sponsor expeditiously (i.e., within 24 hours after learning of the event; see Section 5.4.2 for reporting instructions), irrespective of regulatory seriousness criteria:

- DLTs occurring during the DLT assessment window
- Grade 4 hyperglycemia
- Grade ≥3 symptomatic hyperglycemia
- Grade ≥2 colitis or enterocolitis
- Grade ≥3 diarrhea
- Grade ≥3 rash
- Grade ≥2 pneumonitis
- 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 5.3.1)
- Suspected transmission of an infectious agent by the study drug

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 5.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

5.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

After initiation of study medication, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later (see Section 5.5). After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see Section 5.6).

5.2.2 Eliciting Adverse Event Information

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

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

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

5.2.3 Assessment of Severity and Causality of Adverse Events

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

For each AE and SAE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity, and causality.

Table 14 provides guidance for grading AE severity and Table 15 provides guidance for assessing the causal relationship to the investigational product(s).

The AE grading (severity) scale found in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 will be used for assessing AE severity (see Table 14).

Table 14 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[b]
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[c]
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated
5	Death related to AE	

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

The NCI CTCAE v4.0 can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Note: Regardless of severity, some events may also meet regulatory seriousness criteria. Refer to definition of a serious AE (see Section 5.1.2).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

[b] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[c] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

Table 15 Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon re-challenge. Investigators should apply facts, evidence, or rationales based on scientific principles and clinical judgment to support a causal/contributory association with an investigational product.
NO	AEs will be considered related, unless they fulfill the criteria as specified below. Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study drug). Note: The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities. **Attribution of SAEs will be reviewed on an ongoing basis, and may be changed as additional clinical data emerges (e.g., reversibility of AE, new clinical findings in patient with AE, effects of retreatment, AEs in other patients)**.

AE = adverse event; SAE = serious adverse event.

In addition to assessing causality with respect to study drug, investigators should also assess whether other factors (e.g., disease under study, concurrent illness, concomitant medication, or study procedure) may have caused the event, using similar guidance.

5.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

5.3.1 Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF. Avoid colloquialisms and abbreviations.

There is one Adverse Event eCRF for recording AEs or SAEs.

Only one medical concept should be recorded in the event field on the Adverse Event eCRF.

a. Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the 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 as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

c. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation timepoints. Such AEs should only be recorded once in the eCRF unless their severity changes. If a persistent AE becomes more or less severe it should be recorded on a new AE eCRF with the same AE description but with the new severity recorded.

If a change in intensity of the AE qualifies the event as an SAE per the seriousness criteria in Section 5.1.2, the event should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor per the SAE reporting procedure outlined in Section 5.4.2.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints and subsequently recurs. All recurrent AEs should be recorded separately on an Adverse Event eCRF.

d. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

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

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. 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 not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

Abnormal Liver Enzymes

The finding of an elevated ALT or AST ($>3 \times$ ULN) 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 an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

The most appropriate diagnosis or, if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.1).

e. Deaths

Deaths that occur during the protocol-specified AE reporting period (see Section 5.2.1) that are attributed by the investigator solely to progression of cancer will be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of attribution, will be recorded on an Adverse Event eCRF and expeditiously reported to the Sponsor.

When recording a death, 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. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" on the Adverse Event eCRF.

f. Preexisting Medical Conditions

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

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an 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").

g. Worsening of Cancer

Worsening and/or progression of cancer (including new sites of metastasis) should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

Signs and symptoms clearly associated with the disease under study should not be reported as AEs unless they are any one of the following:

- Newly emergent (i.e., not previously observed in the patient)
- Judged by the investigator to be unusually severe or accelerated
- Judged by the investigator to represent exacerbation of disease-related signs and symptoms caused directly by the study drug

If there is reasonable uncertainty about an AE being caused by disease progression, it should be reported as an AE or SAE as appropriate.

h. Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

i. Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or within 90 days after the last dose of investigational product, a Pregnancy Report eCRF should be completed and submitted electronically via the EDC system to Genentech's Drug Safety Department or its designee within 24 hours of learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. In the event the EDC system is unavailable, a completed paper Pregnancy CRF and Pregnancy fax coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee at the fax numbers listed in Section 5.4.2. Once the EDC system is available, all information will need to be entered and submitted using the EDC system.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on an Adverse Event

eCRF, and expeditiously reported to the Sponsor. After the study period, such events should still be reported expeditiously to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be classified as serious and recorded on an Adverse Event eCRF and expeditiously reported to the Sponsor during the study period. After the study period, such events should still be reported expeditiously to the Sponsor recorded and reported as an SAE.

In the event the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee at the fax numbers listed in Section 5.4.2.

j. Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

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 serious 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).

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST

5.4.1 Reporting Requirements for Fatal/Life-Threatening Serious Adverse Events Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an Adverse Event eCRF within 24 hours as described in Section 5.4.2.

Medical Monitor Contact Information:

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted]

Alternate Telephone No.: +1 (888) 835-2555

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

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to the Sponsor's Safety Risk Management department by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax number provided below. If international fax is not available, the CRF may be sent via email to the address below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Fax No.: +44 122 337 4102

Email: EMEAASIASafetyCentral.SM@ppdi.com

Relevant follow-up information should be submitted to Genentech's Safety Risk Management Department or its designee as soon as it becomes available and/or upon request.

5.5 TYPE AND DURATION OF FOLLOW UP OF PATIENTS AFTER ADVERSE EVENTS

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, another anti-cancer therapy is initiated, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the appropriate Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV) during the study period.

For some SAEs, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

5.6 POST-STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be

related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Genentech Drug Safety on the study Adverse Event eCRF. If the study Adverse Event eCRF is no longer available, the investigator should report the event directly to Genentech Drug Safety via phone at 1-888-835-2555.

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

Genentech 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, Genentech will assess the expectedness of these events using the following reference document:

- Taselisib (GDC-0032) Investigator's Brochure
- *SmPC for fulvestrant, letrozole, or midazolam*

Genentech 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 Genentech as needed.

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Genentech or a Genentech representative:

- U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator
- The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae and evidence of licensure of the Principal Investigator and all subinvestigators
- Complete financial disclosure forms for the Principal Investigator and all subinvestigators listed on the U.S. FDA Form 1572
- Federalwide Assurance number or IRB statement of compliance

- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form
- Genentech or its designee must review any proposed deviations from the sample Informed Consent Form.
- Current laboratory certification of the laboratory performing the analysis (if other than a Genentech-approved central laboratory), as well as current references ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable), IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator
- Country-specific documents, as required

6.2 STUDY COMPLETION

The following data and materials are required by Genentech before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (is other than Genentech-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and subinvestigator, U.S. FDA Form 1572 for each site)
- A signed and dated Protocol Amendment Acceptance Form(s) (if applicable)
- Updated financial disclosure forms for the Principal Investigator and all subinvestigators listed on the U.S. FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

7. ETHICAL CONSIDERATIONS

7.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

7.2 INFORMED CONSENT FORM

Genentech's Sample Informed Consent Form (and sample Child's Assent, if applicable) will be provided to each site. Genentech or its designee must review and approve any proposed deviations from the Sample Informed Consent Form [and Child's Assent, if applicable] or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB/EC-approved Consent Forms must be provided to Genentech for regulatory purposes.

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

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

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

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

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

In the United States, each Informed Consent Form may also include authorization allowing the institution, investigator, subinvestigator and the Sponsor(s) to use and disclose Personal Health information in compliance with the HIPAA of 1996.

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

Optional Research Informed Consent

If archival tissue and/or plasma/serum collection for optional research is approved by the IRB/IEC, the Consent Form entitled "Sample Optional Research Informed Consent Form," will be provided by Genentech to each study site. This form gives patients the option to authorize the collection and use of these samples and personal health information for additional research purposes. Signing of this separate consent form is not required for enrollment in the trial but is required prior to any optional research sample collection. All procedures outlined above for review, approval, processing, and use of Consent Forms also apply to this optional research form.

7.3 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator for review and approval 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 regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Genentech. Investigators are responsible for ensuring that such reports are reviewed

and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's Study File.

7.4 CONFIDENTIALITY

Genentech 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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

7.5 FINANCIAL DISCLOSURE

Investigators will provide Genentech with sufficient, accurate financial information in accordance with local regulations to allow Genentech 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.

8. DATA COLLECTION AND MANAGEMENT

8.1 DATA QUALITY ASSURANCE

Genentech will be responsible for 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 Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

Genentech will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data or other electronic data will be sent directly to Genentech, using the Genentech'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.

8.2 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Genentech representative to inspect study data, patients' medical records, and eCRFs. The Principal Investigator will permit Genentech monitors/representatives and collaborators, the U.S. FDA, other regulatory agencies, Institutional Review Boards, and the respective national or local health authorities to inspect facilities and records relevant to this study.

8.3 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using the Medidata Solutions (New York, NY) RAVE® EDC system. Sites will receive training for appropriate eCRF completion. eCRFs will be submitted electronically to Genentech and should be handled in accordance with instructions from Genentech.

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, 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.

8.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification (SDV) 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 are where 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, patient diaries or 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 the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

8.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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 FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the study monitor, Genentech's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

8.6 STUDY MEDICATION ACCOUNTABILITY

In the United States, only GDC-0032 will be provided by Genentech; sites will procure fulvestrant, letrozole, and midazolam, and these drugs will be reimbursed by Genentech. In non-U.S. countries, all study drugs required for completion of this study will be provided by Genentech. The recipient will acknowledge receipt of the drug by returning

the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to, and disposed of by the study site should be recorded by using the Drug Inventory Log or comparable document.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

8.7 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or 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 regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

8.8 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for Good Clinical Practice (GCP) (see Section 4.9 of the Guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of Genentech. Written notification should be provided to Genentech for transfer of any records to another party or moving them to another location.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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, Informed Consent Forms, 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 Genentech 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 Genentech or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Genentech monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial is sponsored by Genentech, Inc. Study centers in the United States, Canada, and Europe will participate in this study to enroll approximately 611–711 patients. Data will be recorded via an EDC system from Medidata Solutions, Inc. (New York, NY), using electronic Case Report Forms (eCRFs; see Section 8.3). An independent review facility (IRF) will be used for interpretation and central review of FDG-PET imaging in accordance with guidelines that will be detailed in an IRF charter; an imaging manual will be provided to study sites. A central ECG facility will be used for blinded ECG reading and interpretation; an ECG manual will be provided to study sites. A central laboratory will be used to manage PK, PD, and tissue samples.

9.5 *DISSEMINATION* OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, Genentech is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses*, in clinical trial registries of the U.S. National Institutes of Health and the European Medicines Agency,* and in peer-reviewed journals. Genentech will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 7.4 for more details).* For more information, refer to the Roche (Genentech) Global Policy on Sharing of Clinical Trials Data at the following website:

http://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, Genentech 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, Genentech 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 Genentech prior to submission for publication or presentation. This allows Genentech 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, Genentech 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 Genentech 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 Genentech, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by Genentech. 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).

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Appendix A-1
Study Flowchart: Screening and Cycle 1 Assessments for Stage 1

Assessment	Screening [a]	Pretreatment [b]	PK Evaluation Period				Cycle 1				
Cycle Day (Window)	−14 to −1		1	2	3	4	8 (±1)	15 (±1)	16 (±1)	22 (±1)	29 (±1)
Informed consent(s) (−28 to −1 days)	x										
Medical history and demographic data [c]	x										
Complete physical examination [d]	x						x				
Limited physical examination [e]			x					x		x	x
Weight and height (height at screening only)	x		x				x	x		x	x
Vital signs [f]	x		x [g]	x			x	x	x	x	x
ECOG performance status (see Appendix F)	x						x				
12-Lead electrocardiogram [h]	x		x	x				x	x		
Tumor assessment [i]	x										
CBC with differential and platelet count [j]	x						x	x		x	x
Fasting serum or plasma chemistry [k]	x						x	x		x	x
Glycosylated hemoglobin (HBA_{1c})	x										
Fasting insulin and glucose [l]	x		x				x	x		x	x
Fasting lipid profile and amylase [m]	x							x		x	x
Coagulation (INR and aPTT/PTT)	x										
Serum fibrinogen	x										x
Urinalysis (laboratory) [n]	x										
Pregnancy test [o]	x										
Flow cytometry (FACS) [p]	x										
FDG-PET imaging [q]		x									x

Appendix A-1
Study Flowchart: Screening and Cycle 1 Assessments for Stage 1 (cont.)

Assessment	Screening [a]	Pretreatment [b]	PK Evaluation Period				Cycle 1				
Cycle Day (Window)	−14 to −1		1	2	3	4	8 (±1)	15 (±1)	16 (±1)	22 (±1)	29 (±1)
Blood sample for CTCs [r]		x						x			
Blood sample for ctDNA [s]		x									
Optional fresh tumor tissue biopsy [t]		x						x			
Urine PK collection [u]			x	x							
Plasma PK and PD samples [v]			x	x	x	x	x	x	x	x	x
Archival tumor tissue [w]		x									
Pharmacogenetic blood sample (CYP450 genotyping) [v]		x									
GDC-0032 dosing [x]			x				x	x		x	x
Adverse events			x	x	x	x	x	x	x	x	x
Concomitant medications	x [y]		x	x	x	x	x	x	x	x	x

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; FACS = fluorescence-activated cell sorter; FDG-PET = ^{18}fluorodeoxyglucose positron emission tomography; INR = international normalized ratio; PD = pharmacodynamic; PK = pharmacokinetic; PSA = prostate-specific antigen; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

[a] Perform within 14 days prior to Day 1, with the exception of informed consent and the baseline tumor assessment, which may be obtained up to 28 days prior to Day 1. Assessments performed as standard of care before within the time frame required may be used for screening.

[b] May be performed any time during screening after a patient is determined to be eligible for the study and prior to Day 1 of Cycle 1.

[c] Medical history includes clinically significant diseases within the last 5 years, surgeries, cancer history (including tumor characteristics), prior cancer therapies, and procedures. Demographic data includes age, sex, and self-reported race/ethnicity.

[d] A complete physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

[e] Changes from baseline abnormalities should be recorded at each subsequent limited, symptom-directed, physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

Appendix A-1
Study Flowchart: Screening and Cycle 1 Assessments for Stage 1 (cont.)

[f] Vital signs will include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation by pulse oximetry after patient has been in a seated position for ≥ 5 minutes.

[g] Obtain vital signs predose and 2, 4, and 8 hours postdose.

[h] Submit all ECGs to the diagnostic facility for central review. Perform triplicate digital 12-lead ECG at screening. Perform triplicate 12-lead electronic ECGs measurements on Days 1 and 15 of Cycle 1 (predose, and 4, 8, and 24 hours postdose). A ±30-minutes window is acceptable for all timepoints. If QTc prolongation (> 500 msec) is noted, repeat ECG until the prolongation is reversed or stabilized, evaluate for causes of QT prolongation such as electrolyte imbalances, and notify the Medical Monitor.

[i] Assess all sites of disease per RECIST v1.1 at screening. Include PSA, CA-125, CEA, CA19-9, and/or AFP tests, if appropriate. The same imaging method and serum marker tests used at screening must be used throughout the study. A documented standard of care assessment performed within 28 days before Day 1 may be used for screening. See Section 4.5.1.d and Appendices C, D, and E.

[j] CBC includes RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count. The Cycle 1 Day 8 CBC may be obtained up to 24 hours in advance.

[k] Fasting (≥ 10-hour fast) serum chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT.

[l] Collect fasting insulin and glucose sample per schedule provided in Appendix B-1. Glucose levels may be obtained by fingerstick.

[m] Fasting lipid profile includes total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, amylase, and lipase.

[n] Includes specific gravity, pH, glucose, protein, ketones, and blood.

[o] Serum or urine pregnancy test for women of childbearing potential, including premenopausal women who have had a tubal ligation.

[p] Obtain a blood sample for flow cytometry for lymphocyte subsets by FACS (CD19, CD3, CD4, CD8, CD16, and CD56).

[q] Optional for patients in Cohort 1 in Stage 1 (perform only if patients sign the optional consent). Required for all other patients (Cohorts ≥2 in Stage 1). Perform FDG-PET imaging pretreatment (unless performed as a standard of care assessment and within 14 days prior to Cycle 1, Day 1) and at the end of Cycle 1 (between Days 29–35). Perform imaging 1–4 hours after GDC-0032 dose.

[r] Blood will be collected for CTC analysis prior to dosing on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, at the study discontinuation visit, and at the clinic visit subsequent to the first confirmed partial or complete tumor response or progressive disease (per RECIST) for any patient.

[s] Blood will be collected for ctDNA analysis prior to dosing on Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, at the study discontinuation visit, and at clinic visits on Day 1 of every odd numbered cycle (e.g., C7D1) subsequent to confirmed partial or complete tumor responses and/or at progressive disease (per RECIST) for any patient.

[t] Obtain fresh tumor tissue from those patients in Stage 1 who sign the optional Research Informed Consent Form. Perform biopsy before initiation of GDC-0032 (up to 28 days prior to Cycle 1, Day 1). The pretreatment tissue biopsy will be reviewed by a pathologist to determine whether or not the tissue is evaluable. If the pretreatment tissue is evaluable, then a subsequent biopsy will be performed between Days 15 and 21 of Cycle 1, approximately 1–4 hours after the morning dose. If there is only one lesion for both the biopsy and imaging scans, perform the

biopsy immediately after the scan or at least 1 week prior to FDG-PET imaging or other scans. If two different lesions are being biopsied and scanned, then the second lesion may be biopsied anytime between Days 15 and 21.

[u] Urine samples will be collected predose and 0–6 hours and 6–24 hours after dosing on Day 1 of Cycle 1.

[v] Obtain PK/PD and pharmacogenetic samples according to the schedule provided in Appendix B-1; PK blood samples should be prepared to obtain plasma. Exploratory PK/PD analyses will be run on any leftover samples if the patient specifically consents to this optional testing. The pharmacogenetic blood sample may be obtained on Cycle 1 Day 1 prior to dosing.

[w] Archival tissue from any prior tumor excision or biopsy performed at any time during the course of the patient's illness will be requested from the pathology department of origin. Archival tissue availability will not affect the time a patient may start or enroll into the study.

[x] See Section 4.3.2 for instructions on dosing under fasted conditions (Days 1 and 8). On clinic visit days, administer the dose of GDC-0032 in the clinic. On Day 8, dispense a sufficient number of capsules to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on GDC-0032 dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform GDC-0032 accountability.

[y] Record all medications used by patient within 7 days before screening (including prescription, over-the-counter, herbal remedies, and supplements).

Appendix A-2
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohort A

Assessment	Screening [a]	Pretreatment [b]	Cycle 1							
Cycle Day (Window)	−14 to −1		1	2	8 (±1)	9 (±1)	15 (±1)	22(±1)	23 (±1)	29(±1)
Informed consent(s) (−28 to −1 days)	x									
Medical history and demographic data [c]	x									
Complete physical examination [d]	x				x					
Limited physical examination [e]			x				x	x		x
Weight and height (height at screening only)	x		x		x		x	x		x
Vital signs [f]	x		x [g]	x	x	x	x	x	x	x
ECOG performance status (see Appendix F)	x				x					
12-Lead electrocardiogram [h]	x		x	x				x		
Tumor assessment [i]	x									
CBC with differential and platelet count [j]	x				x		x	x		x
Fasting serum or plasma chemistry [k]	x				x		x	x		x
Glycosylated hemoglobin (HBA_{1c})	x									
Fasting insulin and glucose [l]	x		x		x			x		
Fasting lipid profile and amylase [m]	x						x	x		x
Coagulation (INR and aPTT/PTT)	x									
Serum fibrinogen	x									x
Urinalysis (laboratory) [n]	x									
Pregnancy test [o]	x									
Flow cytometry (FACS) [p]	x									
FDG-PET imaging [q]		x								x

Appendix A-2
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohort A (cont.)

Assessment	Screening [a]	Pretreatment [b]	Cycle 1							
Cycle Day (Window)	−14 to −1		1	2	8 (±1)	9 (±1)	15 (±1)	22(±1)	23 (±1)	29(±1)
Blood sample for CTCs [r]		x					x			
Blood sample for ctDNA [s]		x								
Optional fresh tumor tissue biopsy [t]		x					x			
Plasma PK samples [u]			x	x	x	x		x	x	
Archival tumor tissue [v]		x								
Pharmacogenetic blood sample (CYP450 genotyping) [u]		x								
GDC-0032 dosing [w]			x		x		x	x	x	x
Adverse events			x	x	x	x	x	x	x	x
Concomitant medications	x [x]		x	x	x	x	x	x	x	x

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; FACS = fluorescence-activated cell sorter; FDG-PET = ^{18}fluorodeoxyglucose positron emission tomography; INR = international normalized ratio; PK = pharmacokinetic; PSA = prostate-specific antigen; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

[a] Perform within 14 days prior to Day 1, with the exception of informed consent and the baseline tumor assessment, which may be obtained up to 28 days prior to Day 1. Assessments performed as standard of care before within the time frame required may be used for screening.

[b] May be performed any time during screening after a patient is determined to be eligible for the study and prior to Day 1 of Cycle 1.

[c] Medical history includes clinically significant diseases within the last 5 years, surgeries, cancer history (including tumor characteristics), prior cancer therapies, and procedures. Demographic data includes age, sex, and self-reported race/ethnicity.

[d] A complete physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

[e] Changes from baseline abnormalities should be recorded at each subsequent limited, symptom-directed, physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

[f] Vital signs will include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation by pulse oximetry after patient has been in a seated position for ≥5 minutes.

Appendix A-2
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohort A (cont.)

[g] Obtain vital signs predose and 2, 4, and 8 hours postdose.

[h] Submit all ECGs to the diagnostic facility for central review. Perform triplicate digital 12-lead ECG at screening. Perform triplicate 12-lead electronic ECGs measurements on Days 1 and 22 of Cycle 1 (predose, and 4, 8, and 24 hours postdose). A ±30-minutes window is acceptable for all timepoints. If QTc prolongation (>500 msec) is noted, repeat ECG until the prolongation is reversed or stabilized, evaluate for causes of QT prolongation such as electrolyte imbalances, and notify the Medical Monitor.

[i] Assess all sites of disease per RECIST v1.1 at screening. Include PSA, CA-125, CEA, CA19-9, and/or AFP tests, if appropriate. The same imaging method and serum marker tests used at screening must be used throughout the study. A documented standard of care assessment performed within 28 days before Day 1 may be used for screening. See Section 4.5.1.d and Appendices C, D, and E.

[j] CBC includes RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count. The Cycle 1 Day 8 CBC may be obtained up to 24 hours in advance.

[k] Fasting (≥10-hour fast) serum or plasma chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT.

[l] Collect fasting insulin and glucose sample per schedule provided in Appendix B-2. Glucose levels may be obtained by fingerstick.

[m] Fasting lipid profile includes total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, amylase, and lipase.

[n] Includes specific gravity, pH, glucose, protein, ketones, and blood.

[o] Serum or urine pregnancy test for women of childbearing potential, including premenopausal women who have had a tubal ligation.

[p] Obtain a blood sample for flow cytometry for lymphocyte subsets by FACS (CD19, CD3, CD4, CD8, CD16, and CD56).

[q] Perform FDG-PET imaging pretreatment (unless performed as a standard of care assessment and within 14 days prior to Cycle 1, Day 1) and during the last week of Cycle 1. Perform imaging approximately 1–4 hours after GDC-0032 dose.

[r] Blood will be collected for CTC analysis prior to dosing on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, at the study discontinuation visit, and at the clinic visit subsequent to the first confirmed partial or complete tumor response or progressive disease (per RECIST) for any patient.

[s] Blood will be collected for ctDNA analysis prior to dosing on Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, at the study discontinuation visit, and at clinic visits on Day 1 of every odd numbered cycle (e.g., C7D1) subsequent to confirmed partial or complete tumor responses and/or at progressive disease (per RECIST) for any patient. Pretreatment samples may be obtained on Day 1 before dosing.

[t] Obtain paired fresh tumor tissue from those patients who sign the optional Research Informed Consent Form. Perform biopsy before initiation of GDC-0032 (up to 28 days prior to Cycle 1, Day 1). The pretreatment tissue biopsy will be reviewed by a pathologist to determine whether or not the tissue is evaluable. If the pretreatment tissue is evaluable, then a subsequent biopsy will be performed between Days 15 and 21 of Cycle 1, approximately 1–4 hours after the morning dose. If there is only one lesion for both the biopsy and imaging scans, perform the biopsy immediately after the scan or at least 1 week prior to FDG-PET imaging or other scans. If two different lesions are being biopsied and scanned, then the second lesion may be biopsied anytime between Days 15 and 21.

Appendix A-2
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohort A (cont.)

[u] Obtain PK and pharmacogenetic samples according to the schedule provided in Appendix B-2; PK blood samples should be prepared to obtain plasma. Exploratory PK analyses will be run on any leftover samples if the patient specifically consents to this optional testing. The pharmacogenetic blood sample may be obtained on Cycle 1 Day 1 prior to dosing.

[v] Archival tissue from any prior tumor excision or biopsy performed at any time during the course of the patient's illness will be requested from the pathology department of origin. Archival tissue availability will not affect the time a patient may start or enroll into the study.

[w] See Section 4.3.2 for instructions on dosing under fasted (Day 22) or fed conditions (Day 1 or 8). On clinic visit days, administer the dose of GDC-0032 in the clinic. On Day 8, dispense a sufficient number of capsules to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on GDC-0032 dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform GDC-0032 accountability.

[x] Record all medications used by patient within 7 days before screening (including prescription, over-the-counter, herbal remedies, and supplements).

Appendix A-3
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohorts B, D, and G

Assessment	Screening [a]	Pretreatment [b]	Cycle 1				
Cycle Day (Window)	−14 to −1		1	8 (±1)	15 (±1)	16 (±1)	22 (±1)
Informed consent(s) (−28 to −1 days)	x						
Medical history and demographic data [c]	x						
Complete physical examination [d]	x			x			
Limited physical examination [e]			x		x		x
Weight and height (height at screening only)	x		x	x	x		x
Vital signs [f]	x		x [g]	x	x	x	x
ECOG performance status (see Appendix F)	x			x			
12-Lead electrocardiogram [h]	x		x		x		
Tumor assessment [i]	x						
CBC with differential and platelet count [j]	x			x	x		x
Fasting serum or plasma chemistry [k]	x			x	x		x
Glycosylated hemoglobin (HBA_{1c})	x						
Fasting insulin and glucose [l]	x		x	x	x		
Fasting lipid profile and amylase [m]	x				x		x
Coagulation (INR and aPTT)	x						
Serum fibrinogen	x						x
Urinalysis (laboratory) [n]	x						
Pregnancy test [o]	x						
Flow cytometry (FACS) [p]	x						
FDG-PET imaging [q]		x					x

Appendix A-3
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohorts B, D, and G (cont.)

Assessment	Screening [a]	Pretreatment [b]	Cycle 1				
Cycle Day (Window)	−14 to −1		1	8 (±1)	15 (±1)	16 (±1)	22 (±1)
Blood sample for CTCs [r]		x			x		
Blood sample for ctDNA [s]		x					
Optional fresh tumor tissue biopsy [t]		x			x		
Plasma PK samples [u]			x	x	x	x	
Archival tumor tissue [v]		x					
Pharmacogenetic blood sample (CYP450 genotyping) [u]		x					
GDC-0032 dosing [w]			x	x	x		x
Adverse events			x	x	x	x	x
Concomitant medications	x [x]		x	x	x	x	x

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; FACS = fluorescence-activated cell sorter; FDG-PET = ^{18}fluorodeoxyglucose positron emission tomography; INR = international normalized ratio; PK = pharmacokinetic; PSA = prostate-specific antigen; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.

[a] Perform within 14 days prior to Day 1, with the exception of informed consent and the baseline tumor assessment, which may be obtained up to 28 days prior to Day 1. Assessments performed as standard of care before within the time frame required may be used for screening.

[b] May be performed any time during screening after a patient is determined to be eligible for the study and prior to Day 1 of Cycle 1.

[c] Medical history includes clinically significant diseases within the last 5 years, surgeries, cancer history (including tumor characteristics), prior cancer therapies, and procedures. Demographic data includes age, sex, and self-reported race/ethnicity.

[d] A complete physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

[e] Changes from baseline abnormalities should be recorded at each subsequent limited, symptom-directed, physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

[f] Vital signs will include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation by pulse oximetry after patient has been in a seated position for ≥5 minutes.

Appendix A-3
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohorts B, D, and G (cont.)

[g] Obtain vital signs predose only.

[h] Submit all ECGs to the diagnostic facility for central review. Perform triplicate digital 12-lead ECG at screening. Perform triplicate 12-lead electronic ECGs measurements on Days 1 and 15 of Cycle 1 (predose and 3 hours postdose). A ±30-minutes window is acceptable for all timepoints. If QTc prolongation (> 500 msec) is noted, repeat ECG until the prolongation is reversed or stabilized, evaluate for causes of QT prolongation such as electrolyte imbalances, and notify the Medical Monitor.

[i] Assess all sites of disease per RECIST v1.1 at screening. Include PSA, CA-125, CEA, CA19-9, and/or AFP tests, if appropriate. The same imaging method and serum marker tests used at screening must be used throughout the study. A documented standard of care assessment performed within 28 days before Day 1 may be used for screening. See Section 4.5.1.d and Appendices C, D, and E.

[j] CBC includes RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count.

[k] Fasting (≥10-hour fast) serum or plasma chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT.

[l] Collect fasting insulin and glucose sample per schedule provided in Appendix B-3. Glucose levels may be obtained by fingerstick.

[m] Fasting lipid profile includes total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, amylase, and lipase.

[n] Includes specific gravity, pH, glucose, protein, ketones, and blood.

[o] Serum or urine pregnancy test for women of childbearing potential, including premenopausal women who have had a tubal ligation.

[p] Obtain a blood sample for flow cytometry for lymphocyte subsets by FACS (CD19, CD3, CD4, CD8, CD16, and CD56).

[q] Perform FDG-PET imaging pretreatment (unless performed as a standard of care assessment and within 14 days prior to Cycle 1, Day 1) and during the last week of Cycle 1. Perform imaging 1–4 hours after GDC-0032 dose.

[r] Blood will be collected for CTC analysis prior to dosing on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, at the study discontinuation visit, and at the clinic visit subsequent to the first confirmed partial or complete tumor response or progressive disease (per RECIST) for any patient.

[s] Blood will be collected for ctDNA analysis prior to dosing on Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, at the study discontinuation visit, and at clinic visits on Day 1 of every odd numbered cycle (e.g., C7D1) subsequent to confirmed partial or complete tumor responses and/or at progressive disease (per RECIST) for any patient. Pretreatment samples may be obtained on Day 1 before dosing.

[t] Obtain paired fresh tumor tissue from those patients who sign the optional Research Informed Consent Form. Perform biopsy before initiation of GDC-0032 (up to 28 days prior to Cycle 1, Day 1). The pretreatment tissue biopsy will be reviewed by a pathologist to determine whether or not the tissue is evaluable. If the pretreatment tissue is evaluable, then a subsequent biopsy will be performed between Days 15 and 21 of Cycle 1, approximately 1–4 hours after the morning dose. If there is only one lesion for both the biopsy and imaging scans, perform the biopsy immediately after the scan or at least 1 week prior to FDG-PET imaging or other scans. If two different lesions are being biopsied and scanned, then the second lesion may be biopsied anytime between Days 15 and 21.

Appendix A-3
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohorts B, D, and G (cont.)

[u] Obtain PK and pharmacogenetic samples according to the schedule provided in Appendix B-3; PK blood samples should be prepared to obtain plasma. Exploratory PK analyses will be run on any leftover samples if the patient specifically consents to this optional testing. The pharmacogenetic blood sample may be obtained on Cycle 1 Day 1 prior to dosing.

[v] Archival tissue from any prior tumor excision or biopsy performed at any time during the course of the patient's illness will be requested from the pathology department of origin. Archival tissue availability will not affect the time a patient may start or enroll into the study.

[w] On clinic visit days, administer the dose of GDC-0032 in the clinic. On Day 1, dispense a sufficient number of capsules or tablets to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on GDC-0032 dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform GDC-0032 accountability.

[x] Record all medications used by patient within 7 days before screening (including prescription, over-the-counter, herbal remedies, and supplements).

Appendix A-4
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohort C

Assessment	Screening [a]	Pretreatment [b]	Cycle 1					
Cycle Day (Window)	−14 to −1		1	2	9 (±1)	16 (±1)	17 (±1)	23 (±1)
Informed consent(s) (−28 to −1 days)	x							
Medical history and demographic data [c]	x							
Complete physical examination [d]	x				x			
Limited physical examination [e]			x			x		x
Weight and height (height at screening only)	x		x		x	x		x
Vital signs [f]	x		x [g]	x	x	x	x	x
ECOG performance status (see Appendix F)	x				x			
12-Lead electrocardiogram [h]	x		x	x		x	x	
Tumor assessment [i]	x							
CBC with differential and platelet count [j]	x				x	x		x
Fasting serum or plasma chemistry [k]	x				x	x		x
Glycosylated hemoglobin (HBA_{1c})	x							
Fasting insulin and glucose [l]	x		x			x		
Fasting lipid profile and amylase [m]	x					x		x
Coagulation (INR and aPTT)	x							
Serum fibrinogen	x							x
Urinalysis (laboratory) [n]	x							
Pregnancy test [o]	x							
Flow cytometry (FACS) [p]	x							
FDG-PET imaging [q]		x						x

Appendix A-4
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohort C (cont.)

Assessment	Screening [a]	Pretreatment [b]	Cycle 1					
Cycle Day (Window)	−14 to −1		1	2	9 (±1)	16 (±1)	17 (±1)	23 (±1)
Blood sample for CTCs [r]		x				x		
Blood sample for ctDNA [s]		x						
Optional fresh tumor tissue biopsy [t]		x				x		
Plasma PK samples [u]			x	x		x	x	
Archival tumor tissue [v]		x						
Pharmacogenetic blood sample (CYP450 genotyping) [u]		x						
GDC-0032 dosing [w]				x	x	x		x
Midazolam dosing			x			x		
Adverse events			x	x	x	x	x	x
Concomitant medications	x [x]		x	x	x	x	x	x

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; FACS = fluorescence-activated cell sorter; FDG-PET = ^{18}fluorodeoxyglucose positron emission tomography; INR = international normalized ratio; PK = pharmacokinetic; PSA = prostate-specific antigen; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

[a] Perform within 14 days prior to Day 1, with the exception of informed consent and the baseline tumor assessment, which may be obtained up to 28 days prior to Day 1. Assessments performed as standard of care within the time frame required may be used for screening.

[b] May be performed any time during screening after a patient is determined to be eligible for the study and prior to Day 1 of Cycle 1.

[c] Medical history includes clinically significant diseases within the last 5 years, surgeries, cancer history (including tumor characteristics), prior cancer therapies, and procedures. Demographic data includes age, sex, and self-reported race/ethnicity.

[d] A complete physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

[e] Changes from baseline abnormalities should be recorded at each subsequent limited, symptom-directed, physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

Appendix A-4
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohort C (cont.)

[f] Vital signs will include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation by pulse oximetry after patient has been in a seated position for ≥5 minutes.

[g] Obtain vital signs predose and 2, 4, and 8 hours postdose.

[h] Submit all ECGs to the diagnostic facility for central review. Perform triplicate digital 12-lead ECG at screening. Perform triplicate 12-lead electronic ECGs measurements on Days 1 and 16 of Cycle 1 (predose, and 4, 8, and 24 hours postdose). A ±30-minutes window is acceptable for all timepoints. If QTc prolongation (>500 msec) is noted, repeat ECG until the prolongation is reversed or stabilized, evaluate for causes of QT prolongation such as electrolyte imbalances, and notify the Medical Monitor.

[i] Assess all sites of disease per RECIST v1.1 at screening. Include PSA, CA-125, CEA, CA19-9, and/or AFP tests, if appropriate. The same imaging method and serum marker tests used at screening must be used throughout the study. A documented standard of care assessment performed within 28 days before Day 1 may be used for screening. See Section 4.5.1.d and Appendices C, D, and E.

[j] CBC includes RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count.

[k] Fasting (≥10-hour fast) serum of plasma chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT.

[l] Collect fasting insulin and glucose sample per schedule provided in Appendices B-4. Glucose levels may be obtained by fingerstick.

[m] Fasting lipid profile includes total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, amylase, and lipase.

[n] Includes specific gravity, pH, glucose, protein, ketones, and blood.

[o] Serum or urine pregnancy test for women of childbearing potential, including premenopausal women who have had a tubal ligation.

[p] Obtain a blood sample for flow cytometry for lymphocyte subsets by FACS (CD19, CD3, CD4, CD8, CD16, and CD56).

[q] Perform FDG-PET imaging pretreatment (unless performed as a standard of care assessment and within 14 days prior to Cycle 1, Day 1) and during the last week of Cycle 1. Perform imaging 1–4 hours after GDC-0032 dose.

[r] Blood will be collected for CTC analysis prior to dosing on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, at the study discontinuation visit, and at the clinic visit subsequent to the first confirmed partial or complete tumor response or progressive disease (per RECIST) for any patient.

[s] Blood will be collected for ctDNA analysis prior to dosing on Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, at the study discontinuation visit, and at clinic visits on Day 1 of every odd numbered cycle (e.g., C7D1) subsequent to confirmed partial or complete tumor responses and/or at progressive disease (per RECIST) for any patient. Pretreatment samples may be obtained on Day 1 before dosing.

Appendix A-4
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohort C (cont.)

[t] Obtain fresh tumor tissue from those patients who sign the optional Research Informed Consent Form. Perform biopsy before initiation of GDC-0032 (up to 28 days prior to Cycle 1, Day 1). The pretreatment tissue biopsy will be reviewed by a pathologist to determine whether or not the tissue is evaluable. If the pretreatment tissue is evaluable, then a subsequent biopsy will be performed between Days 15 and 21 of Cycle 1, approximately 1–4 hours after the morning dose. If there is only one lesion for both the biopsy and imaging scans, perform the biopsy immediately after the scan or at least 1 week prior to FDG-PET imaging or other scans. If two different lesions are being biopsied and scanned, then the second lesion may be biopsied anytime between Days 15 and 21.

[u] Obtain PK and pharmacogenetic samples according to the schedule provided in Appendices B-4; PK blood samples should be prepared to obtain plasma. Exploratory PK analyses will be run on any leftover samples if the patient specifically consents to this optional testing. The pharmacogenetic blood sample may be obtained on Cycle 1 Day 1 prior to dosing.

[v] Archival tissue from any prior tumor excision or biopsy performed at any time during the course of the patient's illness will be requested from the pathology department of origin. Archival tissue availability will not affect the time a patient may start or enroll into the study.

[w] On clinic visit days, administer the dose of GDC-0032 in the clinic. On Day 2, dispense a sufficient number of capsules to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on GDC-0032 dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform GDC-0032 accountability.

[x] Record all medications used by patient within 7 days before screening (including prescription, over-the-counter, herbal remedies, and supplements).

Appendix A-5
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohorts E and F

Assessment	Screening [a]	Pretreatment [b]	Cycle 1				
Cycle Day (Window)	−14 to −1		1	8 (±1)	15 (±1)	16 (±1)	22 (±1)
Informed consent(s) (−28 to −1 days)	x						
Medical history and demographic data [c]	x						
Complete physical examination [d]	x			x			
Limited physical examination [e]			x		x		x
Weight and height (height at screening only)	x		x	x	x		x
Vital signs [f]	x		x	x	x [g]	x	x
ECOG performance status (see Appendix F)	x			x			
12-Lead electrocardiogram [h]	x		x		x	x	
Tumor assessment [i]	x						
CBC with differential and platelet count [j]	x			x	x		x
Fasting serum or plasma chemistry [k]	x			x	x		x
Glycosylated hemoglobin (HBA_{1c})	x						
Fasting insulin and glucose [l]	x		x	x	x		
Fasting lipid profile and amylase [m]	x				x		x
Coagulation (INR and aPTT)	x						
Serum fibrinogen	x						x
Urinalysis (laboratory) [n]	x						
Pregnancy test [o]	x						
Flow cytometry (FACS) [p]	x						
FDG-PET imaging [q]		x					x

Appendix A-5
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohorts E and F (cont.)

Assessment	Screening [a]	Pretreatment [b]	Cycle 1				
Cycle Day (Window)	−14 to −1		1	8 (±1)	15 (±1)	16 (±1)	22 (±1)
Blood sample for CTCs [r]		x			x		
Blood sample for ctDNA [s]		x					
Optional fresh tumor tissue biopsy [t]		x			x		
Plasma PK samples [u]			x	x	x	x	
Archival tumor tissue [v]		x					
Pharmacogenetic blood sample (CYP450 genotyping) [u]		x					
GDC-0032 dosing [w]			x	x	x		x
Letrozole dosing (Cohort E only) [x]			x	x	x		x
Fulvestrant dosing (Cohort F only) [y]			x		x		
Adverse events			x	x	x	x	x
Concomitant medications	x [z]		x	x	x	x	x

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; FACS = fluorescence-activated cell sorter; FDG-PET = ^{18}fluorodeoxyglucose positron emission tomography; INR = international normalized ratio; PK = pharmacokinetic; PSA = prostate-specific antigen; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

[a] Perform within 14 days prior to Day 1, with the exception of informed consent and the baseline tumor assessment, which may be obtained up to 28 days prior to Day 1. Assessments performed as standard of care before within the time frame required may be used for screening.

[b] May be performed any time during screening after a patient is determined to be eligible for the study and prior to Day 1 of Cycle 1.

[c] Medical history includes clinically significant diseases within the last 5 years, surgeries, cancer history (including tumor characteristics), prior cancer therapies, and procedures. Demographic data includes age, sex, and self-reported race/ethnicity.

[d] A complete physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

[e] Changes from baseline abnormalities should be recorded at each subsequent limited, symptom-directed, physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

Appendix A-5
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohorts E and F (cont.)

[f] Vital signs will include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation by pulse oximetry after patient has been in a seated position for ≥5 minutes.

[g] Obtain vital signs predose and 2, 4, and 8 hours postdose.

[h] Submit all ECGs to the diagnostic facility for central review. Perform triplicate digital 12-lead ECG at screening. Perform triplicate 12-lead electronic ECGs measurements on Day 1 (predose and 3 hours postdose) and Day 15 of Cycle 1 (predose, and 4, 8, and 24 hours postdose). A ± 30-minutes window is acceptable for all timepoints. If QTc prolongation (>500 msec) is noted, repeat ECG until the prolongation is reversed or stabilized, evaluate for causes of QT prolongation such as electrolyte imbalances, and notify the Medical Monitor.

[i] Assess all sites of disease per RECIST v1.1 at screening. Include PSA, CA-125, CEA, CA19-9, and/or AFP tests, if appropriate. The same imaging method and serum marker tests used at screening must be used throughout the study. A documented standard of care assessment performed within 28 days before Day 1 may be used for screening. See Section 4.5.1.d and Appendices C, D, and E.

[j] CBC includes RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count.

[k] Fasting (≥ 10-hour fast) serum or plasma chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT.

[l] Collect fasting insulin and glucose sample per schedule provided in Appendices B-5 and B-6. Glucose levels may be obtained by fingerstick.

[m] Fasting lipid profile includes total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, amylase, and lipase.

[n] Includes specific gravity, pH, glucose, protein, ketones, and blood.

[o] Serum or urine pregnancy test for women of childbearing potential, including premenopausal women who have had a tubal ligation.

[p] Obtain a blood sample for flow cytometry for lymphocyte subsets by FACS (CD19, CD3, CD4, CD8, CD16, and CD56).

[q] Perform FDG-PET imaging pretreatment (unless performed as a standard of care assessment and within 14 days prior to Cycle 1, Day 1) and at during the last week of Cycle 1. Perform imaging 1–4 hours after GDC-0032 dose.

[r] Blood will be collected for CTC analysis prior to dosing on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, at the study discontinuation visit, and at the clinic visit subsequent to the first confirmed partial or complete tumor response or progressive disease (per RECIST) for any patient.

[s] Blood will be collected for ctDNA analysis prior to dosing on Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, at the study discontinuation visit, and at clinic visits on Day 1 of every odd numbered cycle (e.g., C7D1) subsequent to confirmed partial or complete tumor responses and/or at progressive disease (per RECIST) for any patient. Pretreatment samples may be obtained on Day 1 before dosing.

Appendix A-5
Study Flowchart: Screening and Cycle 1 Assessments for Stage 2, Cohorts E and F (cont.)

[t] Obtain fresh tumor tissue from those patients who sign the optional Research Informed Consent Form. Perform biopsy before initiation of GDC-0032 (up to 28 days prior to Cycle 1, Day 1). The pretreatment tissue biopsy will be reviewed by a pathologist to determine whether or not the tissue is evaluable. If the pretreatment tissue is evaluable, then a subsequent biopsy will be performed between Days 15 and 21 of Cycle 1, approximately 1–4 hours after the morning dose. If there is only one lesion for both the biopsy and imaging scans, perform the biopsy immediately after the scan or at least 1 week prior to FDG-PET imaging or other scans. If two different lesions are being biopsied and scanned, then the second lesion may be biopsied anytime between Days 15 and 21.

[u] Obtain PK and pharmacogenetic samples according to the schedule provided in Appendices B-5 and B-6; PK blood samples should be prepared to obtain plasma. Exploratory PK analyses will be run on any leftover samples if the patient specifically consents to this optional testing. The pharmacogenetic blood sample may be obtained on Cycle 1 Day 1 prior to dosing.

[v] Archival tissue from any prior tumor excision or biopsy performed at any time during the course of the patient's illness will be requested from the pathology department of origin. Archival tissue availability will not affect the time a patient may start or enroll into the study.

[w] On clinic visit days, administer the dose of GDC-0032 in the clinic. On Day 1, dispense a sufficient number of capsules to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on GDC-0032 dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform GDC-0032 accountability.

[x] Cohort E only: On clinic visit days, administer the dose of letrozole in the clinic. On Day 1, dispense a sufficient number of letrozole capsules to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on letrozole dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform letrozole accountability.

[y] Cohort F only: Administer the dose of fulvestrant in the clinic.

[z] Record all medications used by patient within 7 days before screening (including prescription, over-the-counter, herbal remedies, and supplements).

Appendix A-6
Study Flowchart: Assessments for Continuation of Treatment beyond Cycle 1 (Stage 1; Stage 2, Cohorts A–G)

Assessment	Cycle 2			Cycles 3–6		Cycles ≥7 Odd-Numbered Cycles	Cycles ≥7 Even-Numbered Cycles	Study Completion/ Early Termination [a]
Cycle Day	1[b]	8	15	1	15	1	1	
Visit Window (Day[s])	±1	±1	±1	±1	±1	±3	±3	±2 Weeks
Complete physical examination [c]	x			x		x	x	
Limited physical examination [d]		x	x		x			x
Weight	x	x	x	x	x	x	x	x
Vital signs [e]	x	x	x	x	x	x	x	x
ECOG performance status (see Appendix F)	x			x		x	x	x
12-Lead electrocardiogram [f]	x			x			x	
Tumor assessment [g]			x		x		x	x
CBC with differential and platelet count [h]	x	x	x	x	x	x	x	x
Fasting serum or plasma chemistry [i]	x	x	x	x	x	x	x	x
Fasting insulin and glucose [j]	x			x		x	x	x
Fasting lipid profile and amylase [k]	x			x			x	x
Serum fibrinogen	x			x			x	x
Flow cytometry (FACS) [l]	x			x			x	x
FDG-PET imaging [m]			x					
Plasma PK samples [n]	x			x		x	x	x
Blood sample for CTCs [o]				x				x
Blood sample for ctDNA [p]				x				x

Appendix A-6
Study Flowchart: Assessments for Continuation of Treatment beyond Cycle 1 (Stage 1; Stage 2, Cohorts A–G) (cont.)

Assessment	Cycle 2			Cycles 3–6		Cycles ≥7 Odd-Numbered Cycles	Cycles ≥7 Even-Numbered Cycles	Study Completion/ Early Termination [a]
Cycle Day	1[b]	8	15	1	15	1	1	
Visit Window (Day[s])	±1	±1	±1	±1	±1	±3	±3	±2 Weeks
Optional fresh tumor tissue biopsy [q]								x
GDC-0032 dosing [r]	x	x	x	x	x	x	x	
Letrozole dosing (Cohort E only) [s]	x	x	x	x	x	x	x	
Fulvestrant dosing (Cohort F only) [t]	x			x		x	x	
Adverse events	x	x	x	x	x	x	x	x [u]
Concomitant medications	x	x	x	x	x	x	x	x

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; FACS = fluorescence-activated cell sorter; FDG-PET = ^{18}fluorodeoxyglucose positron emission tomography; INR = international normalized ratio; PK = pharmacokinetic; PSA = prostate-specific antigen; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

Notes: All assessments should be performed before dosing unless otherwise noted. Some assessments may be done outside the window indicated to accommodate holidays and unforeseen scheduling issues, depending on the assessment, and ongoing safety issues with the trial and with the patient, after approval by the Medical Monitor.

[a] The Study Completion/Early Termination Visit should be performed within 30 days (±2 weeks) after the last dose of GDC-0032.

[b] The end of Cycle 1 visit is the same as the Cycle 2, Day 1 visit. All assessments will be performed and results should be reviewed before dosing for Cycle 2.

[c] A complete physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

[d] Changes from baseline abnormalities should be recorded at each subsequent limited, symptom-directed, physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

[e] Vital signs will include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation by pulse oximetry after patient has been in a seated position for ≥5 minutes.

Appendix A-6
Study Flowchart: Assessments for Continuation of Treatment beyond Cycle 1 (Stage 1; Stage 2, Cohorts A–G) (cont.)

[f] Perform triplicate digital 12-lead ECG after administration of GDC-0032 at the specified visits. On Cycle 2, Day 1, also perform triplicate digital 12-lead ECG prior to administration of GDC-0032. If QTc prolongation (>500 msec) is noted, repeat ECG until the prolongation is reversed or stabilized, evaluate for causes of QT prolongation such as electrolyte imbalances, and notify the Medical Monitor. ECGs must be submitted to the diagnostic facility for central review.

[g] Assess all sites of disease per RECIST v1.1 at the end of Cycle 2 (between Days 22–28) and at the end of each even-numbered cycle thereafter (i.e., every 8 weeks; between Days 22–28). For patients in the study for > 24 cycles, imaging may be performed every 12 weeks. Perform assessments before dosing at the next scheduled cycle. Include PSA or CA-125 tests, if appropriate. The same imaging method and serum marker tests used at screening must be used throughout the study. See Section 4.5.1.d and Appendices C, D, and E. If a patient undergoes an interim tumor evaluation to confirm a partial response (i.e., between 5–7 weeks after previous tumor assessment), the next scheduled tumor assessment may be skipped.

[h] CBC includes RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count.

[i] Fasting (≥10-hour fast) serum or plasma chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT.

[j] Collect fasting insulin and glucose samples per schedule provided in Appendices B-1 to B-6. Glucose levels may be obtained by fingerstick.

[k] Fasting lipid profile includes total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, amylase, and lipase. The assessment may be performed up to 1 week prior to Day 1 of each cycle (i.e., between Days 22–28 of the previous cycle) in order for the test results to be available for the scheduled visit.

[l] Obtain a blood sample for flow cytometry for lymphocyte subsets by FACS (CD19, CD3, CD4, CD8, CD16, and CD56).

[m] Optional for patients in Cohort 1 in Stage 1 (perform only if patients sign the optional consent). Required for all other patients, starting with patients enrolled in Cohort 2 in Stage 1 and for all patients enrolled in Stage 2. Perform imaging at the end of Cycle 2 (between Days 22–28), 1–4 hours after GDC-0032 dose. If the Cycle 1 PET imaging shows no significant changes in tumor FDG uptake from screening, then the FDG-PET imaging in Cycle 2 should not be obtained.

[n] PK samples should be obtained according to the schedule provided in Appendices B-1 to B-6.

[o] Blood will be collected for CTC analysis prior to dosing on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, at the study discontinuation visit, and at the clinic visit subsequent to the first confirmed partial or complete tumor response or progressive disease (per RECIST) for any patient.

[p] Blood will be collected for ctDNA analysis prior to dosing on Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, at the study discontinuation visit, and at clinic visits on Day 1 of every odd numbered cycle (e.g., C7D1) subsequent to confirmed partial or complete tumor responses and/or at progressive disease (per RECIST) for any patient. Pretreatment samples may be obtained on Day 1 before dosing.

[q] Obtain optional fresh tumor tissue upon disease progression from those patients who sign the optional Research Informed Consent Form.

Appendix A-6
Study Flowchart: Assessments for Continuation of Treatment beyond Cycle 1 (Stage 1; Stage 2, Cohorts A–G) (cont.)

[r] On clinic visit days, administer the dose of GDC-0032 in the clinic. On Day 1, dispense a sufficient number of capsules or tablets to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on GDC-0032 dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform GDC-0032 accountability.

[s] Cohort E only: On clinic visit days, administer the dose of letrozole in the clinic. On Day 1, dispense a sufficient number of letrozole capsules to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on letrozole dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform letrozole accountability.

[t] Cohort F only: Administer the dose of fulvestrant in the clinic.

[u] Patients with unresolved adverse events thought to be related to GDC-0032 must be followed as clinically indicated, until the event is resolved or stabilized, another anti-cancer therapy is initiated, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the adverse event.

Appendix A-7
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) *before LPI +6 months*

Assessment	Screening	Pretreatment	Cycle 1			Cycle 2		Cycles ≥3	Treatment Completion [a] (within 30 Days after Last Dose)	Follow-Up
Cycle Day (Window)	28 days prior to C1D1	28 days prior to C1D1	1	8 (± 2 days)	15 (±2 days)	1 (±2 days)	15 (±2 days)	1 (±3 days)		
Informed consent	x									
Medical history and demographic data [b]	x									
Concomitant medications [c]	x		x	x [aa]	x	x	x	x	x	
Adverse events [d]			x	x [aa]	x	x	x	x	x	x
B symptoms (Cohorts T and T2)	x		x			x		x	x	
Vital signs [e]	x		x	x [aa]	x	x	x	x	x	
Complete physical examination, weight [f]	x								x	
Limited physical examination, weight [g]			x		x	x	x	x		
ECOG performance status	x					x		x	x	
Triplicate 12-lead ECG [h]	x				x	x			x	
Tumor (or response) assessment [i]	x		End of Cycles 2, 4, 6, and 8 and every 3 cycles (12 weeks) thereafter						x	

Appendix A-7
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) *before LPI +6 months* (cont.)

Assessment	Screening	Pretreatment	Cycle 1			Cycle 2		Cycles ≥3	Treatment Completion [a] (within 30 Days after Last Dose)	Follow-Up
Cycle Day (Window)	28 days prior to C1D1	28 days prior to C1D1	1	8 (± 2 days)	15 (±2 days)	1 (±2 days)	15 (±2 days)	1 (±3 days)		
Bone scan (Cohorts J, K, L, M, N, P, Q, R, and S) [j]	x		End of Cycles 3, 6, and 8, and every 3 cycles (12 weeks) thereafter							
Bone marrow aspiration and biopsy (Cohorts T and T2)	x		As indicated with tumor assessment only if marrow involvement is present at screening [bb]							
Pregnancy test [k]	x									
CBC with differential and platelets [l]	x		x	x [dd]	x	x	x	x	x	
Fasting serum or plasma chemistry [m]	x		x	x [aa]	x	x	x	x	x	
LDH (Cohorts T and T2)	x		x			x		x	x	
HbA_{1C}	x									
Coagulation (INR, aPTT)	x									
Fasting lipid profile [n]	x		x					x	x	
Urinalysis [o]	x									
Pharmacogenetics sample			x							
FDG-PET (Cohorts L, M, N, Q, R, and S) [z]		x			x		x			
Archival tumor tissue [p]		x								

Appendix A-7
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) *before LPI +6 months* (cont.)

Assessment	Screening	Pretreatment	Cycle 1			Cycle 2		Cycles ≥3	Treatment Completion [a] (within 30 Days after Last Dose)	Follow-Up
Cycle Day (Window)	28 days prior to C1D1	28 days prior to C1D1	1	8 (± 2 days)	15 (±2 days)	1 (±2 days)	15 (±2 days)	1 (±3 days)		
Optional fresh tumor biopsy [q]		x			x				x	
Mandatory PD tumor biopsy (Cohorts N and P)		x			x					
Confirmation of receipt of adequate tissue for *PIK3CA* assessment (Cohort X)		x								
Tumor tissue specimen (Cohort T2) [cc]		x								
Confirmation of *KRAS* wild-type status for Cohort X8		x								
Tissue sample at disease progression *		Tissue taken anytime following disease progression								
Blood sample for ctDNA [r]			x					x	x	
Blood sample for CTC (Cohorts H–P) [s]			x		x			x	x	
Chemokine and cytokine blood sample [t]			x		x				x	
Flow cytometry [u]			x					x	x	

Appendix A-7
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) *before LPI +6 months* (cont.)

Assessment	Screening	Pretreatment	Cycle 1			Cycle 2		Cycles ≥3	Treatment Completion [a] (within 30 Days after Last Dose)	Follow-Up
Cycle Day (Window)	28 days prior to C1D1	28 days prior to C1D1	1	8 (± 2 days)	15 (±2 days)	1 (±2 days)	15 (±2 days)	1 (±3 days)		
Pharmacokinetics sample				See Appendices B-7 to B-14 for Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X						
Fulvestrant administration (Cohorts J, K, L, and M) [v]			x		x	x		x		
Letrozole administration (Cohorts N, P, Q, R, and S) [y]			x			x		x		
GDC-0032 administration in the clinic [w]			x		x	x	x	x		
Follow-up assessment for survival [x]										x

aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; CBC = complete blood count; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTC = circulating tumor cells; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; *EOT = end of treatment;* FFPE = formalin-fixed paraffin-embedded; INR = international normalized ratio; MRI = magnetic resonance image; PD = pharmacodynamic; RBC = red blood cell; WBC = white blood cell.

Note: i) Screening Labs must be valid within 28 days prior to C1D1. ii) Assessments scheduled on the day of study drug administration in the clinic (e.g., Cycle 2 Day 1) should be performed prior to study drug administration, unless otherwise noted. Results should be reviewed prior to the administration of the study drug treatments. *iii) Discontinuation of GDC-0032 treatment, i.e., EOT (GDC-0032), after LPI +6 months (approximately 31 December 2018) will also constitute discontinuation from the study. iv) Patients continuing treatment beyond LPI +6 months will undergo a reduced set of assessments, as outlined in Appendix A-9.*

[a] The visit at which disease progression is recorded may serve as the treatment completion visit.

Appendix A-7
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) *before LPI +6 months* (cont.)

[b] Medical history includes clinically significant diseases within the last 5 years, surgeries, cancer history (including tumor characteristics), prior cancer therapies, and procedures. Demographic data includes age, sex, and self-reported race/ethnicity.

[c] Concomitant medications include prescription medication, over-the-counter preparations, herbal/homeopathic remedies, and therapies used within 7 days prior to screening visit and investigational and anti-cancer therapies used within 28 days prior to Cycle 1 Day 1.

[d] Record adverse events during the study and for 30 days after the last dose of study drug or study discontinuation/termination, whichever is later. Follow any serious adverse events and treatment-related adverse events that are ongoing at treatment completion until the event resolves or stabilizes, patient is lost to follow-up, new anti-tumor treatment is initiated, patient withdraws consent, or it is determined that study treatment or participation is not the cause of the adverse event.

[e] Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation by pulse oximetry after the patient has been in a seated position for $\geq$5 minutes.

[f] Complete physical examination should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems and measurement of weight.

[g] Limited physical examination, including measurement of weight, should be performed to assess and record changes from baseline abnormalities. New or worsened abnormalities should be recorded as adverse events if appropriate. For patients on study for $>$ 24 cycles, limited physical exam may be performed every other cycle.

[h] Submit all ECGs to the diagnostic facility for central review. Perform triplicate digital 12-lead ECGs at screening, on Cycle 1 Day 15 (pre-dose) and Cycle 2 Day 1 (pre-dose) for Cohorts H, J, K, M, N, P, Q, R, T, and X. For Cohorts L and S, perform triplicate digital 12-lead ECGs at screening only. The triplicate ECGs need to be completed within $\pm$30 min of the specified PK sample (i.e., ECGs needs to be time-matched to pre-dose PK sample on Cycle 1 Day 15 and Cycle 2 Day 1). Triplicate digital ECG recordings will be obtained within approximately 2−5 minutes at each specified timepoint. The average of the 3 readings will be used to determine ECG intervals (e.g., PR, QT). ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for $\geq$10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. If QTc prolongation ($>$500 msec) is noted, repeat ECG until the prolongation is reversed or stabilized, evaluate for causes of QT prolongation such as electrolyte imbalances, and notify the Medical Monitor. Perform ECG at the treatment completion visit, and when clinically indicated.

[i] Assess all sites of disease per RECIST v1.1 or the Revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cohort T) at screening ($\leq$28 days prior to Cycle 1 Day 1), the end of Cycles 2, 4, 6, and 8 (between Days 22–28), and at the end of every 3 cycles thereafter (i.e., every 12 weeks between Days 22–28). Cohort T2 will use the Lugano Response Criteria, as detailed in Appendix J. Perform assessments before dosing at the next scheduled cycle. The same imaging method and serum marker tests used at screening must be used throughout the study.

Appendix A-7
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) *before LPI +6 months* (cont.)

[j] Perform a technetium bone scan at screening to rule out bone metastases. In addition, bone disease identified on bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray. In patients without bone-only disease, 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 complete response, if any disease was evident at screening. Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. 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 at the end of Cycles 3, 6, and 8, and every three cycles (12 weeks) thereafter (±1 week for flexibility in the event of isotope shortage). Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. 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, ^{18}F NaF PET scans may be substituted, with the Sponsor's approval. The same modality used at screening should be used throughout the study.

[k] Serum or urine pregnancy test for women of childbearing potential, including premenopausal women who have had a tubal ligation.

[l] includes RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count. Patients enrolled in Cohorts T and T2 should have a weekly CBC for the first two cycles and then on Day 1 of each subsequent cycle or more frequently as clinically indicated.

[m] Fasting (≥10 hours) serum or plasma chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT.

[n] Fasting (≥10 hours) lipid profile should be performed at screening, Day 1 of Cycles 1, 3, and every 3 cycles thereafter and includes total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, amylase, and lipase.

[o] Specific gravity, pH, glucose, protein, ketones, and blood.

[p] Archival tissue from any prior tumor excision or biopsy performed at any time during the course of the patient's illness will be requested from the pathology department of origin. Archival tissue availability will not affect the time a patient may start or enroll into the study; except in Cohort X, archival tissue must be submitted and deemed evaluable prior to enrollment in Cohort X.

[q] Obtain fresh tumor tissue from patients who have signed the optional Research Informed Consent Form or who are enrolled in a mandatory tumor biopsy slot in Cohorts N, P, and X3. Perform biopsy before initiation of GDC-0032 (up to 28 days prior to Cycle 1 Day 1). For Cohorts K and R (5-day on, 2-day off schedule), the on-treatment biopsy will occur between Cycle 1 Day 15 and Cycle 1 Day 19, approximately 1–4 hours after the morning dose of GDC-0032. For other cohorts (H, J, L, M, N, P, Q, S, T, T2, and X), the on-treatment biopsy will occur between Cycle 1 Day 15 and Cycle 1 Day 21, approximately 1–4 hours after the morning dose of GDC-0032.

* Obtain fresh tumor biopsy upon disease progression from those who sign the optional Research Informed Consent Form.

[r] Blood will be collected for ctDNA analysis prior to dosing on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 3 Day 1, Cycle 5 Day 1, at the study discontinuation visit, and at clinic visits on Day 1 of every odd numbered cycle (e.g., C7D1) for any patient. Pretreatment samples may be obtained on Day 1 before dosing.

Appendix A-7
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) *before LPI +6 months* (cont.)

[s] Blood will be collected for CTC analysis for Cohorts H, J, K, L, M, N, and P prior to dosing on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, at the study discontinuation visit, and at the clinic visit subsequent to the first confirmed partial or complete tumor response or progressive disease (per RECIST) for any patient.

[t] Obtain blood sample for plasma cytokine and chemokine analysis. Samples must be collected before dosing on Cycle 1 Day 1, Cycle 1 Day 15, and at the treatment completion visit.

[u] Obtain a blood sample for flow cytometry for lymphocyte subsets by FACS (CD19, CD3, CD4, CD8, CD16, and CD56) prior to dosing on Cycle 1 Day 1, Cycle 3 Day 1, and at the study discontinuation visit.

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

[w] GDC-0032 will be taken orally once daily beginning on Cycle 1 Day 1. For Cohorts H and J, GDC-0032 will be taken on Days 1–21 of each 28-day cycle. For Cohort K, GDC-0032 will be taken on Days 1–5, 8–12, 15–19, and 22–26 of each 28-day cycle. For Cohort L, GDC-0032 will be taken on Days 1–7 and 15–21 of each 28-day cycle. GDC-0032 will be administered in the clinic at each scheduled clinic visit, after the predose assessments and procedures, and at home on all non-clinic visit days. A sufficient number of study drug tablets to last until the next visit, or, at the investigator's discretion, to last until the next administration of fulvestrant. Extra tablets may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., because of inclement weather or distance between the patient's home and study center). Patients will also receive a medication diary. Instruct patient to record the time and date each treatment dose is taken in the diary and to return all unused tablets at each study visit. Collect and review medication diary and unused tablets and assess compliance at each subsequent visit. At the completion visit, do not dispense any additional study drug tablets or provide a new medication diary.

[x] All patients who discontinue from the treatment phase will be followed for survival information and subsequent anti-cancer therapies unless the patient requests to be withdrawn from study survival follow-up. Survival follow-up information will be collected via telephone calls, patient's medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by Genentech.

[y] On Day 1 of each cycle, dispense a sufficient number of letrozole capsules to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on letrozole dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform letrozole accountability.

[z] Perform FDG-PET imaging pretreatment (unless performed as a standard of care assessment and within 14 days prior to Cycle 1, Day 1) and during the last week of Cycle 1. Perform Cycle 1 imaging 1–4 hours after GDC-0032 dose. Perform imaging at the end of Cycle 2 (between Days 22 and 28), 1–4 hours after GDC-0032 dose. If the Cycle 1 PET imaging shows no significant changes in tumor FDG uptake from screening, then the FDG-PET imaging in Cycle 2 should not be obtained.

[aa] Cycle 1, Day 8 office visit for patients in Cohort H at 6-mg tablet dose only.

Appendix A-7
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) *before LPI +6 months* (cont.)

[bb] For patients with bone marrow involvement at screening, a repeat assessment will be performed at least once if there is radiologic evidence of a complete response or if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression).

[cc] Availability of adequate archival or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.1 for details).

[dd] Cohorts T and T2 only.

Appendix A-8
Study Flowchart: Phase II Portion of the Study

Assessment	Screening	Pretreatment	Cycle 1		Cycle 2		Cycles ≥3	Treatment Completion [a] (within 30 Days after Last Dose)	Follow-Up
Cycle Day (Window)	28 days prior to C1D1	28 days prior to C1D1	1	15 (±2 days)	1 (±2 days)	15 (±2 days)	1 (±3 days)		
Informed consent	x								
Medical history and demographic data [b]	x								
Concomitant medications [c]	x		x	x	x	x	x	x	
Adverse events [d]			x	x	x	x	x	x	x
Vital signs [e]	x		x	x	x	x	x	x	
Complete physical examination, weight [f]	x							x	
Limited physical examination, weight [g]			x	x	x	x	x		
ECOG performance status	x				x		x	x	
Triplicate 12-lead ECG [h]	x						x	x	
Tumor assessment [i]	x		End of Cycles 2, 4, 6, and 8 and every 3 cycles (12 weeks) thereafter					x	
Bone scan [j]	x		End of Cycles 3, 6, and 8, and every 3 cycles (12 weeks) thereafter						
Pregnancy test [k]	x								
CBC with differential and platelets [l]	x		x	x	x	x	x	x	
Fasting serum or plasma chemistry [m]	x		x	x	x	x	x	x	

Appendix A-8
Study Flowchart: Phase II Portion of the Study (cont.)

Assessment	Screening	Pretreatment	Cycle 1		Cycle 2		Cycles ≥3	Treatment Completion [a] (within 30 Days after Last Dose)	Follow-Up
Cycle Day (Window)	28 days prior to C1D1	28 days prior to C1D1	1	15 (+2 days)	1 (±2 days)	15 (±2 days)	1 (±3 days)		
HbA_{IC}	x								
Coagulation (INR, aPTT)	x								
Fasting lipid profile [n]	x		x				x	x	
Urinalysis [o]	x								
Archival tumor tissue [p]		x							
Optional fresh tumor biopsy [q]		x			x			x	
Blood sample for ctDNA [r]			x	x			x	x	
Blood sample for CTC [s]			x	x			x	x	
Chemokine and cytokine blood sample [t]			x	x				x	
Pharmacogenetics sample		x							
Pharmacokinetics sample			See Appendix B-14						
Fulvestrant administration [u]			x	x	x		x		
GDC-0032 administration in the clinic [v]			x	x	x	x	x		
Follow-up assessment for survival [w]									x

aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; CBC = complete blood count; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTC = circulating tumor cells; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin-embedded; INR = international normalized ratio; MRI = magnetic resonance image; RBC = red blood cell; WBC = white blood cell.

Appendix A-8
Study Flowchart: Phase II Portion of the Study (cont.)

Note: Assessments scheduled on the day of study drug administration in the clinic (e.g., Cycle 2 Day 1) should be performed prior to study drug administration, unless otherwise noted. Results should be reviewed prior to the administration of the study drug treatments.

[a] The visit at which disease progression is recorded may serve as the treatment completion visit.

[b] Medical history includes clinically significant diseases within the last 5 years, surgeries, cancer history (including tumor characteristics), prior cancer therapies, and procedures. Demographic data includes age, sex, and self-reported race/ethnicity.

[c] Concomitant medications include prescription medication, over-the-counter preparations, herbal/homeopathic remedies, and therapies used within 7 days prior to screening visit and investigational and anti-cancer therapies used within 28 days prior to Cycle 1 Day 1.

[d] Record adverse events during the study and for 30 days after the last dose of study drug or study discontinuation/termination, whichever is later. Follow any serious adverse events and treatment-related adverse events that are ongoing at treatment completion until the event resolves or stabilizes, patient is lost to follow-up, new anti-tumor treatment is initiated, patient withdraws consent, or it is determined that study treatment or participation is not the cause of the adverse event.

[e] Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation by pulse oximetry after the patient has been in a seated position for $\geq$ 5 minutes.

[f] Complete physical examination should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems and measurement of weight.

[g] Limited physical examination, including measurement of weight, should be performed to assess and record changes from baseline abnormalities. New or worsened abnormalities should be recorded as adverse events if appropriate.

[h] Triplicate digital ECG recordings will be obtained within approximately 2−5 minutes at each specified timepoint. The average of the 3 readings will be used to determine ECG intervals (e.g., PR, QT). ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for $\geq$ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. The triplicate ECGs need to be completed with $\pm$ 30 minutes of the specified PK sample (i.e., PK sample needs to be time-matched to ECG). Perform ECGs on Cycle 3 Day 1 and every 3 cycles thereafter (e.g., Day 1 of Cycles 6, 9, etc.), at the treatment completion visit, and when clinically indicated.

[i] Assess all sites of disease per RECIST v1.1 at screening ($\leq$28 days prior to Cycle 1 Day 1), the end of Cycles 2, 4, 6, and 8 (between Days 22−28), and at the end of every 3 cycles thereafter (i.e., every 12 weeks between Days 22−28). Perform assessments before dosing at the next scheduled cycle. The same imaging method and serum marker tests used at screening must be used throughout the study.

Appendix A-8
Study Flowchart: Phase II Portion of the Study (cont.)

[j] Perform a technetium bone scan at screening to rule out bone metastases. In addition, bone disease identified on bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray. In patients without bone-only disease, 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 complete response, if any disease was evident at screening. Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. 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 at the end of Cycles 3, 6, and 8, and every three cycles (12 weeks) thereafter ($\pm$1 week for flexibility in the event of isotope shortage). Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. 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, ^{18}F NaF PET scans may be substituted, with the Sponsor's approval. The same modality used at screening should be used throughout the study.

[k] Serum or urine pregnancy test for women of childbearing potential, including premenopausal women who have had a tubal ligation.

[l] includes RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count.

[m] Fasting ($\geq$10-hour fast) serum or plasma chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT.

[n] Fasting ($\geq$10 hours) lipid profile should be performed at screening, Day 1 of Cycles 1, 3, and every 3 cycles thereafter and includes total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, amylase, and lipase.

[o] Specific gravity, pH, glucose, protein, ketones, and blood.

[p] Archival tissue from any prior tumor excision or biopsy performed at any time during the course of the patient's illness will be requested from the pathology department of origin. Archival tissue availability will not affect the time a patient may start or enroll into the study.

[q] Obtain fresh tumor tissue from patients who have signed the optional Research Informed Consent Form. Perform biopsy before initiation of GDC-0032 (up to 28 days prior to Cycle 1 Day 1). The on-treatment biopsy will occur between Cycle 2 Day 1 and Cycle 2 Day 15, approximately 1–4 hours after the morning dose of GDC-0032. Obtain optional fresh tumor tissue upon disease progression from those patients who sign the optional Research Informed Consent Form.

[r] Blood will be collected for ctDNA analysis prior to dosing on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, Cycle 5 Day 1, at the study discontinuation visit, and at clinic visits on Day 1 of every odd numbered cycle (e.g., Cycle 7 Day 1) subsequent to confirmed partial or complete tumor response and/or at progressive disease (per RECIST) for any patient. Pretreatment samples may be obtained on Day 1 before dosing.

[s] Blood will be collected for CTC analysis prior to dosing on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, at the study discontinuation visit, and at the clinic visit subsequent to the first confirmed partial or complete tumor response or progressive disease (per RECIST) for any patient.

[t] Obtain blood sample for plasma cytokine and chemokine analysis. Samples must be collected before dosing on Cycle 1 Day 1, Cycle 1 Day 15, and at the treatment completion visit.

Appendix A-8
Study Flowchart: Phase II Portion of the Study (cont.)

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

[v] GDC-0032 will be taken orally once daily beginning on Cycle 1 Day 1. GDC-0032 will be administered in the clinic at each scheduled clinic visit, after the predose assessments and procedures, and at home on all non-clinic visit days. A sufficient number of study drug tablets to last until the next visit, or, at the investigator's discretion, to last until the next administration of fulvestrant. Extra tablets may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., because of inclement weather or distance between the patient's home and study center). Patients will also receive a medication diary. Instruct patient to record the time and date each treatment dose is taken in the diary and to return all unused capsules at each study visit. Collect and review medication diary and unused capsules and assess compliance at each subsequent visit. At the completion visit, do not dispense any additional study drug capsules or provide a new medication diary.

[w] All patients who discontinue from the treatment phase will be followed for survival information and subsequent anti-cancer therapies unless the patient requests to be withdrawn from study survival follow-up. Survival follow-up information will be collected via telephone calls, patient's medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by Genentech.

Appendix A-9
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) after LPI +6 Months (Patients Deriving Benefit from GDC-0032)

Assessment	*Day 1 (±3 days) of Each Treatment Cycle*	*Treatment Completion [a] (within 30 Days after Last Dose)*	*Follow-Up*
Concomitant medications [b]	*x*	*x*	
Adverse events [c]	*x*	*x*	*x*
Vital signs [d]	*x*	*x*	
Complete physical examination, weight [e]		*x*	
Limited physical examination, weight [f]	*x*		
ECOG performance status	*x*	*x*	
Monitoring for disease progression	*Perform per institutional standards*		
CBC with differential and platelets [g]	*x*	*x*	
Fasting serum or plasma chemistry [h]	*x*	*x*	
Fasting lipid profile [i]	*x*	*x*	
Fulvestrant administration (Cohorts J, K, L, and M) [j]	*x*		
Letrozole administration (Cohorts N, P, Q, R, and S) [k]	*x*		
GDC-0032 administration in the clinic [l]	*x*		

aPTT =activated partial thromboplastin time; BUN =blood urea nitrogen; CBC =complete blood count; C1D1 =Cycle 1 Day 1; CT =computed tomography; CTC =circulating tumor cells; D =day; ECG =electrocardiogram; ECOG =Eastern Cooperative Oncology Group; FFPE =formalin-fixed paraffin-embedded; INR =international normalized ratio; MRI =magnetic resonance image; PD =pharmacodynamic; RBC =red blood cell; WBC =white blood cell.

Appendix A-9
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) after LPI +6 Months (Patients Deriving Benefit from GDC-0032) (cont.)

Notes: Assessments scheduled on the day of study drug administration in the clinic (e.g., Cycle 2 Day 1) should be performed prior to study drug administration, unless otherwise noted. Results should be reviewed prior to the administration of the study drug treatments.

Survival follow-up will be halted as of LPI +6 months.

[a] *The visit at which disease progression occurs may serve as the treatment completion visit.*

[b] *Concomitant medications include prescription medication, over-the-counter preparations, herbal/homeopathic remedies, and therapies used within 7 days prior to screening visit and investigational and anti-cancer therapies used within 28 days prior to Cycle 1 Day 1.*

[c] *Record adverse events during the study and for 30 days after the last dose of study drug or study discontinuation/termination, whichever is later. Follow any serious adverse events and treatment-related adverse events that are ongoing at treatment completion until the event resolves or stabilizes, patient is lost to follow-up, new anti-tumor treatment is initiated, patient withdraws consent, or it is determined that study treatment or participation is not the cause of the adverse event.*

[d] *Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and oral or tympanic temperature. Oxygen saturation by pulse oximetry after the patient has been in a seated position for ≥5 minutes.*

[e] *Complete physical examination should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems and measurement of weight.*

[f] *Limited physical examination, including measurement of weight, should be performed to assess and record changes from baseline abnormalities. New or worsened abnormalities should be recorded as adverse events if appropriate. For patients on study for > 24 cycles, limited physical exam may be performed every other cycle.*

[g] *Includes RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count. Patients enrolled in Cohorts T and T2 should have a weekly CBC for the first two cycles and then on Day 1 of each subsequent cycle or more frequently as clinically indicated.*

[h] *Fasting (≥10 hours) serum or plasma chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT.*

[i] *Fasting (≥10 hours) lipid profile should be performed at screening, Day 1 of Cycles 1, 3, and every 3 cycles thereafter and includes total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, amylase, and lipase.*

Appendix A-9
Study Flowchart: Stage 2, Cohorts H, J, K, L, M, N, P, Q, R, S, T, T2, and X (X1–X11) after LPI +6 Months (Patients Deriving Benefit from GDC-0032) (cont)

[j] *Fulvestrant will be administered in the clinic as two intramuscular injections of 250 mg each on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle.*

[k] *On Day 1 of each cycle, dispense a sufficient number of letrozole capsules to the patient to last only until the next visit or, at the investigator's discretion, until the next cycle. Instruct the patient on letrozole dosing procedures and diary completion (see Section 4.3.2). Dispense diary and review at subsequent visits and perform letrozole accountability.*

[l] *GDC-0032 will be taken orally once daily beginning on Cycle 1 Day 1. For Cohorts H and J, GDC-0032 will be taken on Days 1–21 of each 28-day cycle. For Cohort K, GDC-0032 will be taken on Days 1–5, 8–12, 15–19, and 22–26 of each 28-day cycle. For Cohort L, GDC-0032 will be taken on Days 1–7 and 15–21 of each 28-day cycle. GDC-0032 will be administered in the clinic at each scheduled clinic visit, after the predose assessments and procedures, and at home on all non-clinic visit days. A sufficient number of study drug tablets to last until the next visit, or, at the investigator's discretion, to last until the next administration of fulvestrant. Extra tablets may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., because of inclement weather or distance between the patient's home and study center). Patients will also receive a medication diary. Instruct patient to record the time and date each treatment dose is taken in the diary and to return all unused tablets at each study visit. Collect and review medication diary and unused tablets and assess compliance at each subsequent visit. At the completion visit, do not dispense any additional study drug tablets or provide a new medication diary.*

Appendix B-1
Pharmacokinetic, Surrogate Pharmacodynamic, and CYP450 Genotyping Flowchart for Patients in Stage 1

Cycle and Day	Timepoint(s)	Assessment/Procedure	Draw Sequence
Cycle 1, Day 1	Predose [a]	GDC-0032 PK	1
		GDC-0032 PD	2
		Insulin and glucose [b]	3
		CYP450 genotyping	4
	0	Administer dose	
	0.5 hour postdose (±5 min)	GDC-0032 PK	1
	1 hour postdose (±5 min)	GDC-0032 PK	1
		GDC-0032 PD	2
	2 hours postdose	GDC-0032 PK	1
		Insulin and glucose [b]	2
	3 hours postdose	GDC-0032 PK	1
		GDC-0032 PD	2
	4 hours postdose	GDC-0032 PK	1
	8 hours postdose	GDC-0032 PK	1
		GDC-0032 PD	2
Cycle 1, Day 2	24 hours postdose (±2 hours)	GDC-0032 PK	1
		GDC-0032 PD	2
Cycle 1, Day 3	48 hours postdose (±2 hours)	GDC-0032 PK	1
Cycle 1, Day 4	72 hours postdose (±2 hours)	GDC-0032 PK	1
Cycle 1, Day 8 (±1 day)	Predose [a]	GDC-0032 PK	1
		GDC-0032 PD	2
		Insulin and glucose	3
	0	Administer dose	
	2 hours postdose (±5 min)	Insulin and glucose [b]	1
Cycle 1, Day 15 (±1 day)	Predose [a]	GDC-0032 PK	1
		GDC-0032 PD	2
		Insulin and glucose [b]	3
	0	Administer dose	
	0.5 hour postdose (±5 min)	GDC-0032 PK	1
	1 hour postdose (±5 min)	GDC-0032 PK	1
		GDC-0032 PD	2
	2 hours postdose	GDC-0032 PK	1
		Insulin and glucose [b]	2

Appendix B-1
Pharmacokinetic, Surrogate Pharmacodynamic, and CYP450 Genotyping Flowchart for Patients in Stage 1 (cont.)

Cycle and Day	Timepoint(s)	Assessment/Procedure	Draw Sequence
Cycle 1, Day 15 (±1 day) (cont'd)	3 hours postdose	GDC-0032 PK	1
		GDC-0032 PD	2
	4 hours postdose	GDC-0032 PK	1
	8 hours postdose	GDC-0032 PK	1
		GDC-0032 PD	2
Cycle1, Day 16 (±1 day)	24 hours postdose (±2 hours)	GDC-0032 PK [c]	1
Cycle 1, Day 22 (±1 day)	Predose [a]	GDC-0032 PK	1
		GDC-0032 PD	2
		Insulin and glucose [b]	3
	2 hours postdose	Insulin and glucose [b]	1
Cycle 1, Day 29 (±1 day)	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
	2 hours postdose	Insulin and glucose [b]	1
Cycles 2–6, Day 1 (±1 day)	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
	2 hours postdose	Insulin and glucose [b]	1
Cycles ≥7, Day 1 (±3 days)	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
	2 hours postdose	Insulin and glucose [b]	1
Study Completion/ Early Termination Visit		GDC-0032 PK	1
		Insulin and glucose [b]	2

PD = pharmacodynamic; PK = pharmacokinetic.

Notes: Except where noted, all sample draw times are ± 10 minutes. For the PK samples, the plasma will be split into two equal aliquots: a primary sample and a backup sample.

Unless otherwise instructed, GDC-0032 should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal), except on days of extensive PK sampling (Days 1 and 15 of Cycle 1) when administration will be under fasted conditions. For administration under fasted conditions, patients will fast overnight for at least 10 hours before dosing and 4 hours postdose and will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of GDC-0032 administration when the capsules will be swallowed whole (not chewed) with 240 mL (8 fluid ounces) of water. On the day of GDC-0032 dosing in the clinic, patients will receive a standard meal at 4 hours postdose.

[a] The blood samples will optimally be obtained within 5 minutes prior to dosing but may be obtained up to 2 hours prior to dosing.

[b] Obtain samples for glucose and insulin only from patients in fasted state. Do not obtain samples from patients who receive a standard meal before dosing. Glucose levels may be obtained by fingerstick.

[c] The PK draw is scheduled prior to the morning dose.

Appendix B-2
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort A (Effect of Food on GDC-0032 Pharmacokinetics in Patients with PIK3CA-Mutant Breast Cancers)

Study Visit	Timepoint(s)	Assessment/Procedure	Draw Sequence
Cycle 1, Day 1	–30 min Predose	Fasting or high-fat meal [a]	
	Predose [b]	GDC-0032 PK	1
		CYP450 genotyping	2
		Insulin and glucose [c]	3
	0	Administer GDC-0032 dose	
	1 hour postdose (±5 min)	GDC-0032 PK	1
	2 hours postdose	GDC-0032 PK	1
	3 hours postdose	GDC-0032 PK	1
		Insulin and glucose [c]	2
	4 hours postdose	GDC-0032 PK	1
	8 hours postdose	GDC-0032 PK	1
Cycle 1, Day 2	24 hours postdose (±2 hours)	GDC-0032 PK	1
Cycle 1, Day 8 (±1 day)	–30 min Predose	Fasting or high-fat meal [a]	
	Predose [b]	GDC-0032 PK	1
		Insulin and glucose [c]	2
	0	Administer GDC-0032 dose	
	1 hour postdose (±5 min)	GDC-0032 PK	1
	2 hours postdose	GDC-0032 PK	1
	3 hours postdose	GDC-0032 PK	1
		Insulin and glucose [c]	2
	4 hours postdose	GDC-0032 PK	1
	8 hours postdose	GDC-0032 PK	1
Cycle 1, Day 9 (±1 day)	24 hours postdose (±2 hours) [d]	GDC-0032 PK	1

Appendix B-2
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort A (Effect of Food on GDC-0032 Pharmacokinetics in Patients with PIK3CA-Mutant Breast Cancers) (cont.)

Study Visit	Timepoint(s)	Assessment/Procedure	Draw Sequence
Cycle 1, Day 22 (±1 day)	Predose [b]	GDC-0032 PK	1
		Insulin and glucose [e]	2
	0	Administer GDC-0032 dose	
	1 hour postdose (±5 min)	GDC-0032 PK	1
	2 hours postdose	GDC-0032 PK	1
	3 hours postdose	GDC-0032 PK	1
		Insulin and glucose [e]	2
	4 hours postdose	GDC-0032 PK	1
	8 hours postdose	GDC-0032 PK	1
Cycle 1, Day 23 (±1 day)	24 hours postdose (±2 hours) [d]	GDC-0032 PK	1
Cycles 2–6, Day 1 (±1 day)	Predose [b]	GDC-0032 PK	1
		Insulin and glucose [e]	2
Cycles ≥7, Day 1 (±3 days)	Predose [b]	GDC-0032 PK	1
		Insulin and glucose [e]	2
Study Completion/Early Termination Visit		GDC-0032 PK	1
		Insulin and glucose [e]	2

PK = pharmacokinetic.

Note: Except where noted, all sample draw times are ± 10 minutes. For the PK samples, the plasma will be split into two equal aliquots: a primary sample and a back-up sample.

[a] Patients will be assigned in an alternating fashion to either Day 1 (subgroup 1: e.g., 1st, 3rd, 5th, and 7th enrolled patients in this cohort) or Day 8 (subgroup 2: e.g., 2nd, 4th, 6th, and 8th enrolled patients in this cohort) for the food-effect assessment. On Day 1 (subgroup 1) or Day 8 (subgroup 2), GDC-0032 will be administered under fed conditions. For dosing under fed conditions, patients will fast overnight for ≥ 10 hours before the standard high-fat meal provided at the study site. Patients should start a standard high fat meal 30 minutes prior to administration of GDC-0032. Patients should consume the whole meal in ≤ 30 minutes. GDC-0032 should be administered 30 minutes after start of the meal with 240 mL (8 ounces) water. No food should be allowed until ≥ 4 hours postdose. Water is not allowed for 1 hour before and 1 hour after drug administration, with the exception of 240 mL (8 fluid ounces) of water intake required for administration of GDC-0032.
On Day 1 (subgroup 1) or Day 8 (subgroup 2) and Day 15, GDC-0032 will be administered under fasting conditions. Patients will fast overnight for at least 10 hours before dosing and 4 hours postdose; patients will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of GDC-0032 administration when the capsules will be

Appendix B-2
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort A (Effect of Food on GDC-0032 Pharmacokinetics in Patients with PIK3CA-Mutant Breast Cancers) (cont.)

swallowed whole (not chewed) with 240 mL (8 fluid ounces) of water. On the day of GDC-0032 dosing in the clinic, patients will receive a standard meal at 4 hours postdose. Unless otherwise instructed, all other doses will be taken on an empty stomach (approximately 1 hour before or 2 hours after a meal).

[b] The blood samples should optimally be obtained within 5 minutes prior to dosing, but may be obtained up to 2 hours prior to dosing.

[c] Samples for glucose and insulin should only be obtained from patients in a fasted state. For patients who receive a standard meal before dosing, do not obtain samples.

[d] The PK draw is scheduled prior to the morning dose.

[e] Patients should be in a fasted state (fasted predose for $\geq$ 10 hours and $\geq$ 4 hours postdose). The postdose sample is not required for patients not being dosed that day.

Appendix B-3
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort B (Patients with PIK3CA-Mutant Solid Tumors), Cohort D (Patients with HER2-Positive Breast Cancers), and Cohort G (Patients with PIK3CA-Amplified Solid Tumors)

Study Visit	Timepoint(s)	Assessment/Procedure	Draw Sequence
Cycle 1, Day 1	Predose [a]	GDC-0032 PK	1
		CYP450 genotyping	2
		Insulin and glucose [b]	3
	0	Administer GDC-0032 dose	
	3 hours postdose	GDC-0032 PK	1
		Insulin and glucose [b]	2
Cycle 1, Day 8	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
Cycle 1, Day 15	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
	0	Administer GDC-0032 dose	
	3 hours postdose	GDC-0032 PK	1
		Insulin and glucose [b]	2
Cycle 1, Day 16	Predose [a]	GDC-0032 PK	1
Cycles 2–6, Day 1 (±1 day)	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
Cycles ≥7, Day 1 (±3 days)	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
Study Completion/Early Termination Visit		GDC-0032 PK	1
		Insulin and glucose [b]	2

PK = pharmacokinetic.

Notes: Except where noted, all sample draw times are ± 10 minutes. For the PK samples, the plasma will be split into two equal aliquots: a primary sample and a back-up sample.

Unless otherwise instructed, GDC-0032 should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal), except on days with scheduled fasting insulin and glucose measures when administration will be under fasted conditions. For administration under fasted conditions, patients will fast overnight for at least 10 hours before dosing and 4 hours postdose and will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of GDC-0032 administration when the doses will be swallowed whole (not chewed) with approximately 240 mL (8 fluid ounces) of water. On the day of GDC-0032 dosing in the clinic, patients will receive a standard meal at 4 hours postdose.

Appendix B-3
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort B (Patients with PIK3CA-Mutant Solid Tumors), Cohort D (Patients with HER2-Positive Breast Cancers), and Cohort G (Patients with PIK3CA-Amplified Solid Tumors) (cont.)

[a] The blood samples should optimally be obtained within 5 minutes prior to dosing, but may be obtained up to 2 hours prior to dosing.

[b] Samples for glucose and insulin should only be obtained from patients in a fasted state (fasted predose for $\geq$ 10 hours and $\geq$ 4 hours postdose). For patients who receive a standard meal before dosing, do not obtain samples.

Appendix B-4
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort C (Effect of GDC-0032 on Midazolam in Patients with Solid Tumors)

Study Visit	Timepoint(s)	Assessment/Procedure	Draw Sequence
Cycle 1, Day 1	Predose [a]	Midazolam PK	1
		Insulin and glucose [b]	2
		CYP450 genotyping	3
	0	Administer midazolam	
	0.5 hour postdose (±5 min)	Midazolam PK	1
	1 hour postdose (±5 min)	Midazolam PK	1
	1.5 hours postdose (±5 min)	Midazolam PK	2
	2 hours postdose	Midazolam PK	1
	4 hours postdose	Midazolam PK	1
	8 hours postdose	Midazolam PK	1
Cycle 1, Day 2	24 hours postdose (±2 hours)	Midazolam PK	1
	Predose [a]	GDC-0032 PK	2
Cycle 1, Day 16	Predose [a]	GDC-0032 PK	1
		Midazolam PK	2
		Insulin and glucose [b]	3
	0	Administer GDC-0032 and midazolam	
	0.5 hour postdose (±5 min)	GDC-0032 PK	1
		Midazolam PK	2
	1 hour postdose (±5 min)	GDC-0032 PK	1
		Midazolam PK	2
	1.5 hour postdose (±5 min)	Midazolam PK	1
	2 hours postdose	GDC-0032 PK	1
		Midazolam PK	2
	3 hours postdose	GDC-0032 PK	1
		Insulin and glucose [b]	2
	4 hours postdose	GDC-0032 PK	1
		Midazolam PK	2
	8 hours postdose	GDC-0032 PK	1
		Midazolam PK	2
Cycle 1, Day 17	24 hours postdose (±2 hours) [c]	GDC-0032 PK	1
		Midazolam PK	2

Appendix B-4
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort C (Effect of GDC-0032 on Midazolam in Patients with Solid Tumors) (cont.)

Study Visit	Timepoint(s)	Assessment/Procedure	Draw Sequence
Cycles 2–6, Day 1 (±1 day)	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
Cycles ≥7, Day 1 (±3 days)	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
Study Completion/Early Termination Visit		GDC-0032 PK	1
		Insulin and glucose [b]	2

PK = pharmacokinetic.

Notes: Except where noted, all sample draw times are ± 10 minutes. For the PK samples, the plasma will be split into two equal aliquots: a primary sample and a back-up sample.

Unless otherwise instructed, GDC-0032 should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal), except on days of extensive PK sampling (Days 1 and 8 of Cycle 1) and on study days with scheduled fasting insulin and glucose measures when administration will be under fasted conditions. For administration under fasted conditions, patients will fast overnight for at least 10 hours before dosing and 4 hours postdose and will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of GDC-0032 (and midazolam) administration when the doses will be swallowed whole (not chewed) with approximately 240 mL (8 fluid ounces) of water. On the day of GDC-0032 dosing in the clinic, patients will receive a standard meal at 4 hours postdose.

[a] The blood samples should optimally be obtained within 5 minutes prior to dosing, but may be obtained up to 2 hours prior to dosing.

[b] Samples for glucose and insulin should only be obtained from patients in a fasted state (fasted predose for ≥ 10 hours and ≥ 4 hours postdose). For patients who receive a standard meal before dosing, do not obtain samples.

[c] The blood draw is scheduled prior to the morning dose.

Appendix B-5
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort E (GDC-0032 in Combination with Letrozole in Patients with Hormone Receptor–Positive Breast Cancer)

Study Visit	Timepoint(s)	Assessment/Procedure	Draw Sequence
Cycle 1, Day 1	Predose [a]	GDC-0032 PK	1
		Letrozole PK	2
		CYP450 genotyping	3
		Insulin and glucose [b]	4
	0	Administer GDC-0032 and letrozole	
	3 hours postdose	GDC-0032 PK	1
		Insulin and glucose [b]	2
Cycle 1, Day 8 (±1 day)	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
Cycle 1, Day 15	Predose [a]	GDC-0032 PK	1
		Letrozole PK	2
		Insulin and glucose [b]	3
	0	Administer GDC-0032 and letrozole	
	1 hour postdose (±5 min)	GDC-0032 PK	1
		Letrozole PK	2
	2 hours postdose	GDC-0032 PK	1
		Letrozole PK	2
	3 hours postdose	GDC-0032 PK	1
		Letrozole PK	2
		Insulin and glucose [b]	3
	4 hours postdose	GDC-0032 PK	1
		Letrozole PK	2
	8 hours postdose	GDC-0032 PK	1
		Letrozole PK	2
Cycle 1, Day 16	24 hours postdose (±2 hours) [c]	GDC-0032 PK	1
		Letrozole PK	2
Cycles 2–6, Day 1 (±1 day)	Predose [a]	GDC-0032 PK	1
		Letrozole PK	2
		Insulin and glucose [b]	3
Cycles ≥7,	Predose [a]	GDC-0032 PK	1

Appendix B-5
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort E (GDC-0032 in Combination with Letrozole in Patients with Hormone Receptor-Positive Breast Cancer) (cont.)

Study Visit	Timepoint(s)	Assessment/Procedure	Draw Sequence
Day 1 (±3 days)		Letrozole PK	2
		Insulin and glucose [b]	3
Study Completion/Early Termination Visit		GDC-0032 PK	1
		Letrozole PK	2
		Insulin and glucose [b]	3

PK = pharmacokinetic.

Notes: Except where noted, all sample draw times are ± 10 minutes. For the PK samples, the plasma will be split into two equal aliquots: a primary sample and a back-up sample.

Unless otherwise instructed, GDC-0032 should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal), except on days with scheduled fasting insulin and glucose measures when administration will be under fasted conditions. For administration under fasted conditions, patients will fast overnight for at least 10 hours before dosing and 4 hours postdose and will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of GDC-0032 administration when the doses will be swallowed whole (not chewed) with approximately 240 mL (8 fluid ounces) of water. On the day of GDC-0032 dosing in the clinic, patients will receive a standard meal at 4 hours postdose.

[a] The blood samples should optimally be obtained within 5 minutes prior to dosing, but may be obtained up to 2 hours prior to dosing.

[b] Samples for glucose and insulin should only be obtained from patients in a fasted state (fasted predose for ≥ 10 hours and ≥ 4 hours postdose). For patients who receive a standard meal before dosing, do not obtain samples.

[c] The PK draw is scheduled prior to the morning dose.

Appendix B-6
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort F (GDC-0032 in Combination with Fulvestrant in Patients with Hormone Receptor–Positive Breast Cancer)

Study Visit	Timepoint(s)	Assessment/Procedure	Draw Sequence
Cycle 1, Day 1	Predose [a]	GDC-0032 PK	1
		Fulvestrant PK	2
		CYP450 genotyping	3
		Insulin and glucose [b]	4
	0	Administer GDC-0032 and fulvestrant	
	3 hours postdose	GDC-0032 PK	1
		Insulin and glucose [b]	2
Cycle 1, Day 8 (±1 day)	Predose [a]	GDC-0032 PK	1
		Insulin and glucose [b]	2
Cycle 1, Day 15	Predose [a]	GDC-0032 PK	1
		Fulvestrant PK	2
		Insulin and glucose [b]	3
	0	Administer GDC-0032 and fulvestrant	
	1 hour postdose (±5 min)	GDC-0032 PK	1
	2 hours postdose	GDC-0032 PK	1
	3 hours postdose	GDC-0032 PK	1
		Insulin and glucose [b]	2
	4 hours postdose	GDC-0032 PK	1
	8 hours postdose	GDC-0032 PK	1
Cycle 1, Day 16	24 hours postdose (±2 hours) [c]	GDC-0032 PK	1
Cycles 2–6, Day 1 (±1 day)	Predose [a]	GDC-0032 PK	1
		Fulvestrant PK	2
		Insulin and glucose [b]	3
Cycles ≥7, Day 1 (±3 days)	Predose [a]	GDC-0032 PK	1
		Fulvestrant PK	2
		Insulin and glucose [b]	3
Study Completion/Early Termination Visit		GDC-0032 PK	1
		Fulvestrant PK	2
		Insulin and glucose [b]	3

Appendix B-6
Pharmacokinetic, Insulin and Glucose, and CYP450 Genotyping Flowchart for Stage 2, Cohort F (GDC-0032 in Combination with Fulvestrant in Patients with Hormone Receptor-Positive Breast Cancer) (cont.)

PK = pharmacokinetic.

Notes: Except where noted, all sample draw times are ± 10 minutes. For the PK samples, the plasma will be split into two equal aliquots: a primary sample and a back-up sample.

Unless otherwise instructed, GDC-0032 should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal), except on days with scheduled fasting insulin and glucose measures when administration will be under fasted conditions. For administration under fasted conditions, patients will fast overnight for at least 10 hours before dosing and 4 hours postdose and will refrain from drinking water from 1 hour before and until 1 hour after dosing, with the exception of GDC-0032 administration when the doses will be swallowed whole (not chewed) with approximately 240 mL (8 fluid ounces) of water. On the day of GDC-0032 dosing in the clinic, patients will receive a standard meal at 4 hours postdose.

[a] The blood samples should optimally be obtained within 5 minutes prior to dosing, but may be obtained up to 2 hours prior to dosing.

[b] Samples for glucose and insulin should only be obtained from patients in a fasted state (fasted predose for ≥ 10 hours and ≥ 4 hours postdose). For patients who receive a standard meal before dosing, do not obtain samples.

[c] The PK draw is scheduled prior to the morning dose.

Appendix B-7
Pharmacokinetic Sample Collection: Phase I, Stage 2, Cohorts H and X Patients

Study Visit	Time	Event
Cycle 1, Day 15	0–4 hours prior to GDC-0032 administration	Predose plasma sample for GDC-0032
	3 hours (± 60 minutes) post–GDC-0032 administration.	Plasma sample for GDC-0032
Cycle 2, Day 1	0–4 hours prior to GDC-0032 administration	Predose plasma sample for GDC-0032
Cycle 6, Day 1	0–4 hours prior to GDC-0032 administration	Predose plasma sample for GDC-0032

Note: See Appendix B-10 for PK sample collection for Cohort X3 patients with head and neck cancers who are taking GDC-0032 as suspension.

Appendix B-8
Pharmacokinetic Sample Collection: Phase I, Stage 2, Cohorts J, K, and M Patients

Study Visit	Time	Event
Cycle 1, Day 15	0–4 hours prior to fulvestrant and GDC-0032 administration	Predose plasma sample for fulvestrant Predose plasma sample for GDC-0032
	3 hours (±60 min) post–GDC-0032 administration.	Plasma sample for GDC-0032
Cycle 2, Day 1	0–4 hours prior to fulvestrant and GDC-0032 administration	Predose plasma sample for fulvestrant Predose plasma sample for GDC-0032
Cycle 6, Day 1	0–4 hours prior to fulvestrant and GDC-0032 administration	Predose plasma sample for fulvestrant Predose plasma sample for GDC-0032

Appendix B-9
Pharmacokinetic Sample Collection: Phase I, Stage 2, Cohorts N, P, Q, and R Patients

Study Visit	Time	Event
Cycle 1, Day 15	0–4 hours prior to letrozole and GDC-0032 administration	Predose plasma sample for letrozole Predose plasma sample for GDC-0032
	3 hours (±60 minutes) post–GDC-0032 administration.	Plasma sample for GDC-0032
Cycle 2, Day 1	0–4 hours prior to letrozole and GDC-0032 administration	Predose plasma sample for letrozole Predose plasma sample for GDC-0032
Cycle 6, Day 1	0–4 hours prior to letrozole and GDC-0032 administration	Predose plasma sample for letrozole Predose plasma sample for GDC-0032

Appendix B-10
Pharmacokinetic Sample Collection: Phase I, Stage 2, Cohort X3 (Head and Neck Cancer) Patients Taking GDC-0032 as Suspension

Cycle and Day	Timepoint(s)	Assessment/Procedure
Cycle 1, Day 1	Pre-dose [a]	Plasma sample for GDC-0032
	0	Administer dose
	0.5 hour post-dose (± 5 min)	Plasma sample for GDC-0032
	1 hour post-dose (± 5 min)	Plasma sample for GDC-0032
	2 hours post-dose	Plasma sample for GDC-0032
	3 hours post-dose	Plasma sample for GDC-0032
	4 hours post-dose	Plasma sample for GDC-0032
	8 hours post-dose	Plasma sample for GDC-0032
Cycle 1, Day 2	24 hours post-dose b (± 2 hours) [b]	Plasma sample for GDC-0032
Cycle 1, Day 15 (± 1 day)	Pre-dose [a]	Plasma sample for GDC-0032
	0	Administer dose
	0.5 hour post-dose (± 5 min)	Plasma sample for GDC-0032
	1 hour post-dose (± 5 min)	Plasma sample for GDC-0032
	2 hours post-dose	Plasma sample for GDC-0032
	3 hours post-dose	Plasma sample for GDC-0032
	4 hours post-dose	Plasma sample for GDC-0032
	8 hours post-dose	Plasma sample for GDC-0032
Cycle 1, Day 16 (± 1 day)	24 hours post-dose (± 2 hours) [b]	Plasma sample for GDC-0032
Cycle 2, Day 1	0–4 hours prior to GDC-0032 administration	Pre-dose plasma sample for GDC-0032
Cycle 6, Day 1	0–4 hours prior to GDC-0032 administration	Pre-dose plasma sample for GDC-0032

[a] The blood samples should optimally be obtained within 5 minutes prior to dosing, but may be obtained up to 2 hours prior to dosing.

[b] The PK draw is scheduled prior to the morning dose.

Note: Except where noted otherwise, all sample draw times are ±10 minutes.

Appendix B-11
Pharmacokinetic Sample Collection: Phase I, Stage 2, Cohort L Patients

Study Visit	Time	Event
Cycle 1, Day 1	3 hours (± 60 min) post–GDC-0032 administration	Plasma sample for GDC-0032
Cycle 2, Day 1	0–4 hours prior to fulvestrant and GDC-0032 administration	Predose plasma sample for fulvestrant
Cycle 6, Day 1	0–4 hours prior to fulvestrant and GDC-0032 administration	Predose plasma sample for fulvestrant

Appendix B-12
Pharmacokinetic Sample Collection: Phase I, Stage 2, Cohort S Patients

Study Visit	Time	Event
Cycle 1, Day 1	3 hours (± 60 min) post–GDC-0032 administration	Plasma sample for GDC-0032
Cycle 2, Day 1	0–4 hours prior to letrozole and GDC-0032 administration	Predose plasma sample for letrozole
Cycle 6, Day 1	0–4 hours prior to letrozole and GDC-0032 administration	Predose plasma sample for letrozole

Appendix B-13
Pharmacokinetic Sample Collection: Phase I, Stage 2, Cohorts T and T2 Patients

Study Visit	Time	Event
Cycle 1, Day 15	0–4 hours prior to GDC-0032 administration	Predose plasma sample for GDC-0032
	3 hours (± 60 minutes) post–GDC-0032 administration.	Plasma sample for GDC-0032
Cycle 2, Day 1	0–4 hours prior to GDC-0032 administration	Predose plasma sample for GDC-0032
Cycle 6, Day 1	0–4 hours prior to GDC-0032 administration	Predose plasma sample for GDC-0032

Appendix B-14
Pharmacokinetic Sample Collection: Phase II Patients

Study Visit	Time	Event
Cycle 1, Day 1	0–4 hours prior to fulvestrant and GDC-0032 administration	Predose plasma sample for fulvestrant Predose plasma sample for GDC-0032
Cycle 1, Day 15	0–4 hours prior to fulvestrant and GDC-0032 administration	Predose plasma sample for fulvestrant Predose plasma sample for GDC-0032
	4 hours (± 30 minutes) post–GDC-0032 administration.	Plasma sample for GDC-0032
Cycle 2, Day 1	0–4 hours prior to fulvestrant and GDC-0032 administration	Predose plasma sample for fulvestrant Predose plasma sample for GDC-0032
Cycle 6, Day 1	0–4 hours prior to fulvestrant and GDC-0032 administration	Predose plasma sample for fulvestrant Predose plasma sample for GDC-0032

Appendix C
Response Evaluation Criteria in Solid Tumors (RECIST): 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/lymph nodes will be categorized as measurable or non-measurable as described below.

a. 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 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.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 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

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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.

mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. 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.

Target Lesions: Specifications by Methods of Measurements

a. 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.

Appendix C
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

b. 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.

Appendix C
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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 ≥ 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.

Appendix C
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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

a. 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.
- 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

b. 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. (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.

c. 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.

- Complete response (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).

Appendix C
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

- 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
- Progressive disease (PD): Unequivocal progression of existing non-target lesions
- The appearance of one or more new lesions is also considered progression.

d. 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.

Bone-Only Disease: Since bone lesions are not considered measurable, patients with bone-only disease will be evaluated for progression only. Progression is defined as the appearance of new lytic lesions or other new bone destruction thought to be related to cancer by X-ray, CT scan or MRI, or a bone event requiring intervention (surgery) if not associated with trauma or other obvious cause. Changes in bone scan or ^{18}F NaF PET

scan should not be used to define progression. Any changes in bone imaging should be evaluated radiographically by X-ray, CT scan, or MRI to ascertain the presence of bone destruction versus a healing reaction. The appearance of new lesions on bone scan or ^{18}F NaF PET scan may constitute progressive disease if associated with clinical symptoms suggestive of disease progression. The occurrence of a pathologic fracture at a site previously recognized for bone disease may constitute progressive disease if not associated with trauma or other obvious cause. Bone pain requiring radiation will constitute progressive disease. Increase in pain at a site of previously recognized bone disease may constitute progressive disease if it is persistent and not associated with other obvious cause.

e. 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.

Evaluation of Response

a. 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.

Appendix C
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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.

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 trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. 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 C
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. 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–Table 3.

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 D
Criteria for PSA Response and Progression for Prostate Cancer Patients

Adapted from Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 1999;17:3461–7.

PSA Response Criteria

A PSA response is defined as a PSA decline of $\geq 50\%$, which must be confirmed by a second PSA value ≥ 4 weeks later. The baseline PSA should be a measurement within 2 weeks before starting therapy. PSA response commences on the date of the first 50% decline in PSA.

Criteria for Definition of PSA Progression

PSA Progression

An increasing PSA may be the only marker of presumed progressive disease. In patients whose PSA has not decreased, progressive disease is defined as a $> 50\%$ increase over baseline (on study), provided that the increase in the absolute PSA level is ≥ 5 ng/mL and that it is confirmed by a second value. There is no limit on the time that elapses between the first documentation of progression and the confirmatory value. In patients whose PSA has decreased, progressive disease occurs when PSA increases by $> 50\%$ over the nadir, provided that the increase is ≥ 5 ng/mL and is confirmed.

Time to PSA Progression

PSA progression may occur before clinical progression. The start of the time to PSA progression is the day treatment is initiated. The date of PSA progression is the date of the first PSA measurement that fulfills the criteria for PSA progression.

Appendix E
Response Criteria for Patients with Ovarian Cancer Who Have Evaluable but Non-Measurable Disease

Patients with evaluable but non-measurable disease are eligible for this study. Their response will be evaluated according to changes in CA-125 and clinical or radiologic observations as described below. Baseline CA-125 is the last measurement prior to starting treatment. Response or progressive disease must be confirmed no less than 4–8 weeks following initial response.

Complete response is defined by both of the following:

- A decrease in CA-125 to within the institutional normal limits and < 40 IU/mL
- No clinical or radiologic evidence of disease

Partial response is defined by both of the following:

- A $> 50\%$ decrease in CA-125 from baseline
- No clinical or radiologic evidence of new lesions

Stable disease is defined as both the following:

- Any change in CA-125 that does not meet the criteria for complete or partial response or for progressive disease
- No clinical or radiologic evidence of new lesions

Progressive disease is defined by either of the following:

- Per the Gynecologic Cancer Intergroup (GCIG) Criteria for Evaluation of Progression according to CA-125 (November 2005), progression or recurrence based on serum CA 125 levels will be defined on the basis of a progressive serial elevation of serum CA 125, according to the following criteria:
  - A. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 $\geq 2 \times$ ULN on two occasions at least 1 week apart, or
  - B. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 $\geq 2 \times$ the nadir value on two occasions at least 1 week apart, or
  - C. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 $\geq 2 \times$ ULN on two occasions at least 1 week apart.
- Clinical or radiologic evidence of new lesions

Appendix F
ECOG Performance Status Scale

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 G
Assessment of FDG-PET Responses

FDG-PET assessments will be used to address one of the exploratory objectives of the study. The outcome measure for this objective will be based on the maximum standard uptake value (SUV_{max}) of up to five regions of interest (ROIs). The tumor ROIs will be identified for each patient on pretreatment PET imaging and must correspond to a subset of the target lesions for analysis of the patient's pretreatment CT scans per RECIST. Additional criteria for selection of ROI on PET imaging will be provided in the Imaging Review Charter.

Determination of PET response will be according to modified European Organization for Research on the Treatment of Cancer (EORTC) definitions (Young et al. 1999). Specifically, the SUV_{max} of each ROI on the on-treatment scans will be compared with its SUV_{max} on the corresponding pretreatment scan and the percent change will be determined. In the event of more than one ROI, the overall percent change in SUV_{max} will be the arithmetic mean of the percent changes in SUV_{max} for each of the ROIs ($mSUV_{max}$).

PET responses will be defined as follows:

- Progressive disease (PET-PD): percent increase of $>20\%$ in $mSUV_{max}$ or the development of a new lesion with an SUV_{max} above background and not explained by another cause (e.g., infection)
- Stable disease (PET-SD): percent increase of $\leq 20\%$ in $mSUV_{max}$ or a percent decrease of $\leq 20\%$ in $mSUV_{max}$
- Partial response (PET-PR): percent decrease of $>20\%$ in $mSUV_{max}$
- Complete response (PET-CR): SUV_{max} indistinguishable from background in all ROIs (i.e., complete disappearance of all PET lesions)

Other methods of analyzing and interpreting the PET imaging data may also be explored.

FDG-PET Imaging

All PET imaging are to be obtained using a combined PET/CT scanner. The image acquisition system must remain consistent throughout all scans for the same patient. Whole-body PET images should extend from the orbital meatus to the proximal femurs. Technical details of the PET scans will be described in an imaging charter.

Plasma PK and PD samples that are scheduled on visits when PET imaging are performed should be obtained before each PET imaging. Blood glucose levels will be obtained immediately prior to FDG-PET imaging. The times of each of these tests and the time of the most recent study drug dose will be recorded on the appropriate eCRFs. All FDG-PET imaging will be collected for evaluation by a central review facility and by Genentech.

Appendix H
Instructions for Scans in the Event of Isotope Shortage

Over the last 20 years there have be intermittent, severe shortages of Tc-99m generators. The most recent one occurred in 2009/2010 when the two reactors supplying the majority of generators (Chalk River Reactor, Canada, and High Flux Reactor, The Netherlands) were repeatedly down for maintenance and repairs. Both reactors are now functioning and there are currently no shortages expected.

Throughout that last shortage, added flexibility in the bone scan imaging schedule of $\pm$7 days has been found sufficient to maintain imaging of clinical trial patients (at times by scheduling them in the evenings or at the weekend).

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, with the approval of the Sponsor. In this case, an ^{18}F NaF PET scan must be performed at screening and, in patients with bone-only disease visible only by ^{18}F NaF PET scan, must be repeated at end of Cycles 3, 6, 8, and every 3 cycles thereafter.

If any challenges in the continued bone scan imaging of patients on this protocol is suspected or anticipated the Sponsor or the Imaging Core Facility should be contacted immediately.

Appendix I
Modified Response and Progression Criteria–Non-Hodgkin's Lymphoma Cohort T

SELECTION OF TARGET LESIONS

Up to six of the largest dominant nodes or tumor masses should be selected according to all of the following (ideally a minimum of three lesions should be chosen):

- Clearly measurable in at least two perpendicular dimensions
- If possible, they should be from disparate regions of the body.
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

SELECTION OF NON-TARGET LESIONS

Non-target lesions will be qualitatively assessed at each subsequent time point. All of the sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions. Examples of non-target lesions include:

- All bone lesions, irrespective of the modality used to assess them
- Lymphangitis of the skin or lung
- Cystic lesions
- Splenomegaly and hepatomegaly
- Irradiated lesions
- Measurable lesions beyond the maximum number of six chosen as target lesions
- Groups of lesions that are small and numerous
- Pleural/pericardial effusions and/or ascites
- For this study, a significant increase in existing pleural effusions, ascites, or other fluid collections will be considered sufficient evidence of progression and will not require cytological proof of malignancy. Effusions, ascites, or other fluid collections will be followed as non-target lesions.

  Existing effusions/ascites: Effusions, ascites, or other fluid collections will be followed as non-target lesions. At each time point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed.

  New effusions/ascites: Significant new effusions, ascites, or other fluid collections that are radiographically suggestive of malignancy should be recorded as new lesions.

Appendix I
Modified Response and Progression Criteria–Non-Hodgkin's Lymphoma Cohort T (cont.)

REPORTING CONVENTIONS

UNABLE TO EVALUATE (UE) LESION CATEGORY

This category is reserved for target and non-target lesions that are deemed unevaluable because 1) subsequent (post-baseline) examinations had not been performed, 2) lesions could not be evaluated due to poor radiographic technique or poorly defined margins, or 3) lesions identified at baseline were not at a subsequent timepoint.

Examples of UE lesions are a lung lesion in the hilum obstructing the bronchus and causing atelectasis of the lobe, or a hypodense liver lesion that becomes surrounded by fatty infiltration. In both examples, the boundaries of the lesion can be difficult to distinguish. Every effort should be made to assign measurements to lesions that develop less distinct margins because they become much smaller. Another example is the instance when lesions identified at baseline were not imaged at a subsequent timepoint. Lesions that cannot be measured or evaluated will be classified for that timepoint as UE.

If a target lesion is classified as UE post-baseline, the sum of the products of the diameters (SPD)/area (whichever applies) of the target lesions cannot accurately be determined for that timepoint, a response of complete response (CR), partial response (PR), or stable disease (SD) cannot be assigned for that timepoint and the response assessment will be UE unless unequivocal progression is determined on the basis of non-target or new lesions or the evaluable target lesions.

Progressive disease (PD) can be determined without evaluation of all sites of disease based on the greatest tumor dimension (GTD), area, or SPD for target lesions, evaluation of unequivocal progression in non-target lesions, or observation of a new lesion within the available radiographic or clinical assessments.

TOO SMALL TO MEASURE (TSTM) LESION CATEGORY

Any target lesion findings identified on baseline images, which at a subsequent timepoint decreases in size to < 5 mm in any dimension, should be categorized as TSTM. The lesion, node, or mass should be assigned measurements of 5 mm × 5 mm (for the GTD and the short axis) on the source document for the purpose of calculating the area. If that lesion increases in size to ≥ 5 mm in any dimension afterwards, its true size (GTD and short axis) should be recorded. The purpose of the assigned value for the measurement is the acknowledgment that small findings are not accurately measured.

Appendix I
Modified Response and Progression Criteria–Non-Hodgkin's Lymphoma Cohort T (cont.)

Timepoint Response

Target Lesions	Non-Target Lesions	New Lesions [a]	Timepoint Response
CR	CR	No	CR
CR	SD	No	PR
CR	UE	No	UE
PR	UE	No	UE
PR	CR	No	PR
PR	SD	No	PR
SD	UE	No	UE
SD	CR	No	SD
SD	SD	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
UE	Non-PD	No	UE
UE	UE	No	UE
CR	NA[c]	No	CR
PR	NA[c]	No	PR
SD	NA[c]	No	SD
NA[b]	SD	No	SD
NA[b]	CR	No	CR
NA[b]	UE	No	UE
NA[b]	NA[c]	No	UE

CR = complete response; NA= not applicable; PD = progressive disease; PR = partial response; SD = stable disease; UE = unable to evaluate.

Note: Modified from Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.

[a] Identification of new lesions at a post-baseline timepoint will result in a response assessment of PD. If an identified new lesion subsequently becomes UE, the timepoint response will be recorded as PD unless the new lesion has proven to have resolved.

[b] No target lesions identified at baseline.

[c] No non-target lesions identified at baseline.

Appendix I
Modified Response and Progression Criteria–Non-Hodgkin's Lymphoma Cohort T (cont.)

COMPLETE REMISSION

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy

2a. Typically 18fluorodeoxyglucose (FDG)-avid lymphoma: In patients with no pre-treatment positron emission tomography (PET) scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: In patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size ($\leq$ 1.5 cm in their greatest transverse diameter for nodes $>$ 1.5 cm before therapy). Previously involved nodes that were 1.1–1.5 cm in their long axis and $>$ 1.0 cm in their short axis before treatment must have decreased to $<$ 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate ($>$ 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a complete remission until data become available demonstrating a clear difference in patient outcome.

PARTIAL REMISSION

1. $\geq$ 50% decrease in SPD of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: a) they should be clearly measurable in at least two perpendicular dimensions; b) if possible, they should be from disparate regions of the body; c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Appendix I
Modified Response and Progression Criteria–Non-Hodgkin's Lymphoma Cohort T (cont.)

2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exceptions of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a partial remission if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria but who have persistent morphologic bone marrow involvement will be considered partial responders.

6. No new sites of disease should be observed (e.g., nodes > 1.5 cm in any axis).

7. Typically FDG-avid lymphoma: For patients with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by > 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

STABLE DISEASE

1. Failing to attain the criteria needed for complete remission or partial remission but not fulfilling those for progressive disease (see below)

2. Typically FGD-avid lymphomas: The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Appendix I
Modified Response and Progression Criteria–Non-Hodgkin's Lymphoma Cohort T (cont.)

RELAPSED DISEASE (AFTER COMPLETE REMISSION) OR PROGRESSIVE DISEASE (FOR PATIENTS WITH PARTIAL REMISSION OR STABLE DISEASE)

Lymph nodes should be considered abnormal if the long axis is $>$ 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1–1.5 cm, it should be considered abnormal only if its short axis is $>$ 1.0. Lymph nodes $\leq$ 1.0 cm by $\leq$ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion $>$ 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size; increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes or in a single involved node or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq$ 50% and to a size of 1.5 $\times$ 1.5 cm or $>$ 1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node $>$ 1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems ($<$ 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease.

Adapted from Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579−86.

Appendix J
Lugano Response Criteria for DLBCL Cohort T2

In this study, a PET-CT–based complete response requires normal bone marrow by morphology for patients with bone marrow involvement at baseline. If indeterminate by morphology, immunohistochemistry should be negative. Additionally, the designation of PET-CT–based PR requires that CT-based response criteria for a CR or PR be met in addition to the PET-CT–based response criteria for a PR. This modified response should be entered in addition to the Lugano PET-CT–Based and CT–Based Responses defined in the table below.

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Appendix J
Lugano Response Criteria for DLBCL Cohort T2 (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to six target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm×5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0×0 mm
		For a node >5 mm×5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable

Appendix J
Lugano Response Criteria for DLBCL Cohort T2 (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to six dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Appendix J
Lugano Response Criteria for DLBCL Cohort T2 (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Progressive disease	Progressive metabolic disease	Progressive disease requires at least one of the following
Individual target nodes/nodal masses	Score 4 or 5 [b] with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisting non-measured lesions

Appendix J
Lugano Response Criteria for DLBCL Cohort T2 (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

Appendix J
Lugano Response Criteria for DLBCL Cohort T2 (cont.)

[a] [a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured; dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.