PROTOCOL

TITLE:	**A PHASE I, MULTICENTER, OPEN-LABEL PREOPERATIVE, SHORT-TERM WINDOW STUDY OF GDC-9545 IN POSTMENOPAUSAL WOMEN WITH STAGE I–III OPERABLE, ESTROGEN RECEPTOR-POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	GO40987
VERSION NUMBER:	4
EUDRACT NUMBER:	2018-003798-85
IND NUMBER:	132673
NCT NUMBER:	*NCT03916744*
TEST PRODUCT:	GDC-9545 (RO7197597)
MEDICAL MONITOR:	[redacted] *M.D., M.P.H.*
SPONSOR:	Genentech, Inc.
APPROVAL FINAL:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
07-Apr-2020 03:05:35	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on title page	France	5	See electronic date stamp on title page
		Belgium	4	See electronic date stamp on title page
3	12 September 2019	France	4	22 November 2019
		Belgium	3	15 November 2019
		United Kingdom	2	10 April 2019
1	21 December 2018	—	—	—

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol GO40987, Version 3 has been amended primarily to reflect the increase of 30 patients in the GDC-9545 30 mg treatment cohort to provide additional pharmacodynamic data [redacted]. These changes are as follows:

- The total number of patients in the GDC-9545 30 mg treatment cohort has been increased to 45 patients to enable a better evaluation of Ki67 expression change at that dose level. A corresponding increase has been made to the total number of patients enrolled in the study (now 75 patients) (Sections 3.1, 4.1, 6.1, and 9.4; Figure 1 and Table 4).
- The projected length of study has been amended to approximately 30 months (Section 3.2).

The following sections have been amended for consistency with institutional practice:

- Language has been modified to clarify that confirmation of available tissue sample is required prior to Day 1 of treatment, rather than confirmation of tissue shipment to the central laboratory (Sections 4.1.1 and 4.5.9; Appendix 1).
- Language related to vital sign measurement has been amended to clarify that temperature may be measured according to institutional practice (Section 4.5.4).

Other changes made to the protocol are as follows:

- Language has been added to clarify that the post-surgery visit should be performed on Day 43 ($\pm$1 week) or prior to the initiation of another anti-cancer therapy, whichever occurs first (Figure 1 and Appendix 1).
- The number of tissue slides requested at screening has been revised to approximately 15 slides for consistency with the preferred number of slides for analysis (Sections 4.1.1 and 4.5.9).
- A reference to next-generation sequencing performed by Foundation Medicine, which had inadvertently been retained in protocol amendment Version 3, has been removed (Section 4.5.9).
- A global change has been made throughout the protocol to update the Medical Monitor, including emergency contact information (Section 5.4.1).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE I, MULTICENTER, OPEN-LABEL PREOPERATIVE, SHORT-TERM WINDOW STUDY OF GDC-9545 IN POSTMENOPAUSAL WOMEN WITH STAGE I–III OPERABLE, ESTROGEN RECEPTOR-POSITIVE BREAST CANCER**
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SPONSOR:	Genentech, Inc.

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

Principal Investigator's Name (print)

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by PPD.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE I, MULTICENTER, OPEN-LABEL PREOPERATIVE, SHORT-TERM WINDOW STUDY OF GDC-9545 IN POSTMENOPAUSAL WOMEN WITH STAGE I–III OPERABLE, ESTROGEN RECEPTOR-POSITIVE BREAST CANCER**
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NCT NUMBER:	*NCT03916744*
TEST PRODUCT:	GDC-9545 (RO7197597)
PHASE:	Phase I
INDICATION:	Stage I–III Operable, Estrogen Receptor–Positive Breast Cancer
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the pharmacodynamics, pharmacokinetics, safety and biologic activity of GDC-9545 in patients with Stage I–III operable estrogen receptor (ER)-positive (HER2-negative) untreated breast cancer. Specific objectives and corresponding endpoints for the study are outlined below.

Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of GDC-9545 when administered in this patient population:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v.5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results, including ECGs

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to evaluate the GDC-9545 PK profile on the basis of the following endpoint:

- Plasma concentration of GDC-9545 at steady state

Activity Objective

The activity objective for this study is to make a preliminary assessment of the activity of GDC-9545 on the basis of the following endpoint:

- Change from baseline in tumor cell proliferation measured by Ki67 expression between pre- and post-treatment samples

Biomarker Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to GDC-9545 (i.e., predictive biomarkers), can provide evidence of GDC-9545 activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in blood and tumor tissue and safety, PK, activity, or other biomarker endpoints
- Cancer-related biomarkers in tumor tissue including DNA mutational status, RNA expression levels, DNA copy number and protein expression
- Modulation of ER and progesterone receptor (PR) protein levels and ER target genes through analysis of paired pre-dose and on-treatment fresh tumor biopsies

Study Design

Description of Study

This is a Phase I, open-label, multicenter, preoperative study to assess changes in Ki67 levels and to evaluate the pharmacodynamics, pharmacokinetics, safety, and biologic activity of GDC-9545 in postmenopausal patients with Stage I–III operable ER-positive (HER2-negative) untreated breast cancer. Approximately 75 patients are expected be enrolled in this study, at approximately 20–30 investigative sites globally.

The study consists of a screening period of up to 28 days; a treatment period of approximately 14 days, including a day for surgery; and a minimum follow-up period of 28 days. Patients will be assigned to one of three treatment cohorts (10, 30, and 100 mg). GDC-9545 will be administered once daily up to and including the day of surgery (if allowed per local process) on Day 15 ($\pm$2 days).

All patients will be required to provide a pretreatment tumor tissue sample. Archival tumor tissue from prior diagnostic formalin-fixed, paraffin-embedded cores (FFPE) may be used; however, if archival tissue is not available or is determined to be unsuitable for required testing, the patient will undergo a tumor biopsy. For the purpose of enrollment, ER, PR, and HER2 will be locally determined prior to beginning of study treatment. Patients who are not evaluable for the primary activity analysis as defined in the protocol will be replaced.

Surgery will take place on Day 15 ($\pm$2). If surgery must be delayed $>$2 days, the Medical Monitor should be consulted. Surgery should be performed within 24 hours after the last dose of GDC-9545, if possible, to best observe PD knockdown with GDC-9545 in the surgical specimen. In lieu of surgical specimen, a biopsy on Day 14 may be obtained. The surgical specimen is not required if biopsy is obtained on Day 14.

All patients will be closely monitored for adverse events throughout the study and for at least 28 days after the final dose of study treatment. Adverse events will be graded according to NCI CTCAE v5.0. In addition to the safety assessments conducted at scheduled clinic visits, patients will be contacted for a general assessment of adverse events at 24 hours post-surgery by telephone, if applicable.

To assess the steady-state concentrations of GDC-9545, a blood sample will be taken at surgery.

If a patient misses more than one dose or the patient's surgery is delayed beyond the allowable window, the Medical Monitor should be consulted about possible replacement.

Number of Patients

Approximately 75 postmenopausal women with HER2-negative, ER-positive, Stage I–III operable untreated breast cancer will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Women age $\geq$18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment

- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor ≥ 1.5 cm in largest diameter by ultrasound
  - Stage I–III operable breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease [e.g., large tumors, clinically positive axillary lymph nodes] signs and symptoms)
- ER-positive tumor and HER2-negative breast cancer as per local laboratory testing
- Postmenopausal status defined as one of the following:
  - Prior bilateral surgical oophorectomy
  - Age ≥ 60 years
  - Age < 60 years and amenorrhea 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and estradiol levels and follicle-stimulating hormone levels in the postmenopausal range
- Breast cancer eligible for primary surgery
- Submission of a representative tumor tissue specimen

  A FFPE tumor specimen in a paraffin block (preferred) or *approximately* 15 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If less than 12 slides are available, the patient may still be eligible for the study after Medical Monitor approval has been obtained. Confirmation of *available tissue sample* is required prior to Day 1 of treatment. If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, tumor tissue must be obtained from a biopsy performed at screening. A biopsy may also be performed at screening if a patient's archival tissue test results do not meet eligibility criteria. Refer to the protocol for additional information on tumor specimens collected at screening.
- Eastern Cooperative Oncology Group Performance Status ≤ 1
- Adequate organ function as defined by the following criteria:
  - ANC ≥ 1500/μL
  - Platelets ≥ 100,000/μL
  - AST and serum ALT ≤ 3 × upper limit of normal (ULN)
  - Total serum bilirubin ≤ 1.5 × ULN

    Inclusion of patients with increased serum indirect bilirubin (≤ 3 × ULN) due to Gilbert's syndrome is permitted.
  - Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate ≥ 50 mL/min/1.73 m^2

Exclusion Criteria

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

- Diagnosis of inflammatory breast cancer
- Diagnosis of bilateral breast cancer
- Concurrent use of hormone replacement therapies
- Previous systemic or local treatment for the primary breast cancer currently under investigation (including surgery, radiotherapy, cytotoxic and endocrine treatments)
- Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to study entry
- Current treatment with any systemic anti-cancer therapies
- Major surgery within 4 weeks prior to enrollment
- Radiation therapy within 2 weeks prior to enrollment

- Diagnosis of any secondary malignancy within 3 years prior to enrollment, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
- Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or upper gastrointestinal surgery including gastric resection
- Known HIV infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., hepatitis B or hepatitis C virus), current alcohol abuse, or cirrhosis
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
- History of allergy to GDC-9545 or any of its excipients
- Any condition requiring anticoagulants, such as warfarin, heparin, or thrombolytic drugs
- History of documented hemorrhagic diathesis or coagulopathy
- History or presence of symptomatic bradycardia
- Baseline heart rate ≤ 55 bpm prior to enrollment
- History or presence of sick sinus syndrome
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction
- QT interval corrected through use of Fridericia's formula >470 ms demonstrated by at least two ECGs >30 minutes apart
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval
- History or presence of uncontrolled hypothyroidism
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs.

Length of Study

The total length of the study, from screening to end of the study, is expected to be approximately *30* months.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product for this study is GDC-9545. GDC-9545 will be administered (orally) once daily continuing up to and including the day of surgery. Patients are allowed to take their final dose of GDC-9545 in the morning on the day of surgery if allowed per local process.

Statistical Methods

Primary Analysis

The final analysis will be performed after LPLV and subsequent data cleaning. The safety analysis will be based on the safety-evaluable population, and activity analysis will be based on the patients who completed study treatment. All summaries will be presented according to the assigned dose level and cohort. In general, data will be summarized as warranted, and listings will be used in place of tables when the samples sizes are small. Continuous variables will be summarized using means, standard deviations, median, and ranges; categorical variables will be summarized using counts and percentages.

Determination of Sample Size

This study is intended to obtain preliminary safety, PK, PD, and activity information. The sample sizes do not reflect any explicit power and type I error considerations.

The range of mean Ki67 expression changes are from 66% (Opportune) to 76% (IMPACT) for 2-week treatment. The planned enrollment for this study is approximately 75 patients. $At\ least$ 15 patients per cohort will provide a more robust safety profile as well as sample size for preliminary assessment of activity based on Ki67 expression.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AI	aromatase inhibitors
AUC	area under the concentration-time curve
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating-tumor DNA
DDIs	drug–drug interaction
DLTs	dose-limiting toxicity
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
ER	estrogen receptor
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded cores
FNA	fine-needle aspiration
FSH	follicle-stimulating hormone
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LBD	ligand-binding domain
LPLV	last patient, last visit
MTD	maximum tolerated dose
NCI	National Cancer Institute
NGS	next-generation sequencing
PD	pharmacodynamic
PK	pharmacokinetic
PLD	phospholipidosis
PR	progesterone receptor
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository

Abbreviation	Definition
SERD	selective estrogen receptor degraders
SERM	selective estrogen receptor modulator
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

Breast cancer is the most frequent cancer diagnosed in women, with an estimated global incidence of 1.67 million new cases reported in 2012 (Ferlay et al. 2013). Breast cancer accounts for approximately 15% (approximately 522,000 cases) of all cancer deaths.

Approximately 80% of all breast cancers express the estrogen receptor (ER) factor, and the vast majority of these are dependent on ER for tumor growth and progression. Modulation of estrogen activity and/or synthesis is the mainstay of therapeutic approaches in women with ER-positive breast cancer. However, despite the effectiveness of available endocrine therapies such as ER antagonists (e.g., tamoxifen) and aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane) many patients ultimately relapse or develop resistance to these agents.

There is mounting evidence that *ESR1* mutations are an important driver of resistance to endocrine treatment (Jeselsohn et al. 2015). While *ESR1* mutations are relatively rare in primary breast cancer, they are more prevalent in metastatic cancers, especially in patients previously treated with aromatase inhibitors, implying that the mutations are acquired (Reinert et al. 2018). *ESR1* mutations result in the ER becoming constitutively active in the absence of estrogen ligand rendering endocrine therapies such as aromatase inhibitors (AI) and tamoxifen ineffective (Robinson et al. 2013; Jeselsohn et al. 2014).

In contrast to AIs and tamoxifen, selective estrogen receptor degraders (SERD) or antagonists are efficacious against these ligand independent, constitutively active ER-mutated receptors and have shown substantial therapeutic benefit. This was first shown in the SoFEA trial, a Phase III randomized study in postmenopausal patients with hormone receptor-positive locally advanced or metastatic breast cancer comparing fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors (Johnston et al. 2013). Subgroup analysis of plasma from the SoFEA trial revealed that patients with *ESR1* mutations had an improved progression-free survival (PFS) of 5.7 months with fulvestrant compared to 2.6 months with exemestane (hazard ratio [HR] = 0.52; 95% CI: 0.30, 0.92; p = 0.02) (Fribbens et al. 2016). This suggested that unlike an AI (exemestane), a SERD (fulvestrant) was active in those patients harboring an *ESR1* mutation.

A SERD (fulvestrant) has also shown benefit over an AI (anastrozole) in frontline patients prior to the formation of *ESR1* mutations. The FALCON study was a Phase III, randomized, double-blind trial that treated de novo locally advanced or metastatic breast cancer hormone receptor–positive patients with either fulvestrant or anastrozole (Robertson et al. 2016). Fulvestrant was associated with a statistically significant improvement in PFS compared with anastrozole (HR = 0.797; 95% CI: 0.637, 0.999; p = 0.0486). Median PFS was 16.6 months (95% CI: 13.83, 20.99 months) with

fulvestrant and 13.8 months (95% CI: 11.99, 16.59 months) with anastrozole (difference in medians: 2.8 months).

Unfortunately, fulvestrant has poor pharmacokinetic (PK) properties, requiring intramuscular injection; therefore, new agents with superior bioavailability, pharmacokinetics, and more potent activity against the ER, including *ESR1* mutations, are needed to further delay disease progression and/or overcome resistance to the currently available endocrine therapies and ultimately prolong survival in women with ER-positive breast cancer.

1.2 BACKGROUND ON GDC-9545

GDC-9545 is a potent, orally bioavailable, small-molecule therapeutic agent that is being developed for the treatment of patients with ER-positive breast cancer. GDC-9545 antagonizes the effects of estrogens via competitive binding to the ligand-binding domain (LBD) of both wild-type and mutant ER with nanomolar potency. Upon binding, GDC-9545 induces an inactive conformation to the ER LBD, as measured by displacement of co-activator peptides. In addition to its direct antagonist properties, the mechanism of action of GDC-9545 includes reducing levels of ERα protein through proteasome-mediated degradation. Degradation of ER is hypothesized to enable full suppression of ER signaling, which is not achieved by first-generation ER therapeutics such as tamoxifen, which display partial agonism. GDC-9545 potently inhibits the proliferation of multiple ER-positive breast cancer cell lines in vitro, including cells engineered to express clinically relevant mutations in ER.

In vivo, GDC-9545 exhibited dose-dependent anti-tumor activity in xenograft models of ER-positive breast cancer, including in a patient-derived xenograft model that harbors an *ESR1* mutation (ER.Y537S). The efficacious dose range was 0.1–10 mg/kg/day, and all doses were well tolerated. Fulvestrant, when dosed according to a clinically relevant dosing scheme, was less efficacious than GDC-9545 in the assessed xenograft models. Thus, GDC-9545 demonstrated robust nonclinical activity in ER-positive breast cancer models of *ESR1*-wildtype– and *ESR1*-mutation–bearing disease.

1.2.1 Nonclinical

1.2.1.1 Pharmacokinetics and Metabolism

After a single IV administration to rats, dogs, and monkeys, GDC-9545 was found to have a low to moderate clearance, a large volume of distribution, and a terminal elimination half-life of 7–24 hours. Oral bioavailability was moderate in rats and dogs (41%–55%) and low (17%) in monkeys. In vitro data showed that plasma protein binding of GDC-9545 was high across all species, ranging from 98% to 99% bound.

In vitro metabolite identification experiments showed that UGT1A4-mediated glucuronidation was the major in vitro metabolic pathway of GDC-9545. The contribution from CYP450 isoforms was minor and included both CYP3A4 and CYP2C9. No human-specific metabolites in mouse, rat, rabbit, dog, monkey and human hepatocytes were detected.

In vitro CYP inhibition studies in human liver microsomes and induction studies in human hepatocytes suggest a low-to-moderate potential for drug–drug interactions (DDIs). GDC-9545 directly inhibited CYP3A4 with 50% inhibitory concentration (IC_{50}) values of 6.5 μM (midazolam 1'-hydroxylation) and 26 μM (testosterone 6β-hydroxylation); IC_{50} for CYP2B6 and CYP2C8 inhibition were 13 μM and 21 μM, respectively. GDC-9545 showed weak metabolism dependent inhibition of CYP2C9.

1.2.1.2 Toxicology

Four-week Good Laboratory Practice repeat-dose oral toxicity studies in female rats and monkeys with integrated assessments of neurologic (rats, monkey), respiratory (monkey), and cardiovascular (monkey) function were conducted to characterize the nonclinical safety profile of GDC-9545.

In the rat study, GDC-9545 was tolerated at all dose levels (10, 30, and 100 mg/kg) with adverse effects predominantly in the kidneys and liver at 100 mg/kg. Similar but minimal histopathologic findings were also observed in the kidney of 1 rat at 30 mg/kg. Additional findings at 100 mg/kg included lymphoid depletion, thymic atrophy, decreased salivary and pancreatic zymogens, gastric erosion, and atrophy of fat in skin; all were considered likely secondary to stress or declining condition in this dose level. At ≥30 mg/kg, scattered skeletal muscle degeneration was also noted in myofibers affected by phospholipidosis (PLD). Pharmacologically-mediated findings in reproductive organs included gross findings in the ovaries and uterus; organ weight changes in the ovaries, uterus, and pituitary gland; and microscopic findings in the ovaries, uterus, cervix, vagina, mammary gland, and clitoral gland. The maximum tolerated dose (MTD) in rats was considered to be 100 mg/kg.

In the monkey study (20, 60, and 200 mg/kg), the MTD was considered to be 60 mg/kg as the high dose of 200 mg/kg was not tolerated with 2 monkeys, which were euthanized early due to moribund condition. Adverse effects were primarily observed at the high dose level of 200 mg/kg, and lack of tolerability was attributed to kidney and liver injury and inanition. Pharmacologically mediated findings in reproductive organs included gross findings in the ovaries and uterus, organ weight changes in the ovaries and uterus, and microscopic findings in the ovaries, uterus, cervix, vagina, and mammary gland.

In both rats and monkeys, there was a dose-dependent PLD observed in numerous organs at exposures that were higher than those anticipated at the human starting dose in Phase I (at least 44-fold and 6-fold based on area under the

concentration–time curve [AUC], respectively), with adverse organ effects largely confined to the kidney and liver. Although associated with the observation of PLD, it is unclear whether these toxicities were caused by PLD. In rats, PLD was not noted at 10 mg/kg (18-fold exposure factor), but increased in incidence and severity from 30 to 100 mg/kg. In monkeys, dose-responsive PLD was present at all doses but was limited to minimal changes in the lung at 20 mg/kg (6-fold exposure factor).

The translatability of PLD from nonclinical species to patients is not certain (Reasor et al. 2006). Drugs such as tamoxifen and palbociclib have not demonstrated any clinical concerns in spite of their PLD findings in nonclinical studies; thus, it is unclear whether GDC-9545-related PLD observed nonclinically will translate into a clinical finding in humans and whether this will have any clinical sequelae if it does. Although GDC-9545 was associated with PLD in multiple tissues in both rats and monkeys, there was no light microscopic evidence of involvement of critical organs such as heart, eyes, or neurons in these studies (Chatman et al. 2009). There is currently no qualified biomarker for assessment of PLD in the clinical setting although bis(monoacylglycerol)phosphate is being suggested as a potential biomarker; however, the function of the organs in which GDC-9545–related PLD may have been associated with toxicity in the 28-day rat and cynomolgus monkey studies (liver and kidney) is readily monitorable in the clinic using standard laboratory assessments.

No respiratory or neurobehavioral abnormalities were detected in rats or cynomolgus monkeys during the 4-week repeat-dose toxicity studies, with the exception of decreased locomotor activity that was only observed in rats at the high dose of 100 mg/kg/day.

Following 28-day oral administration to rats and monkeys, the increases in systemic exposure of GDC-9545 were dose proportional. Based on the nature and reversibility of clinical signs, clinical pathology, and histopathology findings, the severely toxic dose for 10% of animals (STD_{10}) for rats was defined as 100 mg/kg, with corresponding maximum plasma concentration (C_{max}) and AUC from 0 to 24 hours (AUC_{0-24}) values of 6560 ng/mL and 143,000 ng • hr/mL, respectively. In monkeys, the highest non-severely toxic dose was defined as 60 mg/kg/day, with corresponding C_{max} and AUC_{0-24} values of 841 ng/mL and 16,200 ng • hr/mL, respectively, due to the clinical signs and moribundities present at 200 mg/kg/day.

In summary, results from the nonclinical toxicity and safety pharmacology studies completed to date provide a robust characterization of the toxicity profile of GDC-9545 and support administration to patients with cancer. Overall, the nonclinical findings are consistent with the anti-estrogenic mode of action of GDC-9545.

Refer to the GDC-9545 Investigator's Brochure for additional details.

1.2.2 Clinical Summary

As of the data cutoff date of 1 February 2019, a total of 55 postmenopausal women with locally advanced or metastatic ER-positive (HER2-negative) breast cancer, including 29 patients in single-agent dose escalation, 6 patients in palbociclib-combination dose escalation, and 20 patients in single-agent dose expansion, had received at least one dose of GDC-9545 in Study GO39932. During dose escalation, 4 single-agent cohorts of 3 patients each were enrolled at 10-, 30-, 90-, and 250-mg doses, given once daily. To acquire additional PK, pharmacodynamic (PD), and safety data, up to 7 additional patients were enrolled to backfill single-agent dose-escalation cohorts at 10-, 30-, and 90-mg doses. The single-agent dose escalation completed enrollment in October 2018. No dose limiting toxicities (DLTs), related serious adverse events, or adverse events of special interest were reported. The MTD was not determined. Two dose levels of GDC-9545 were chosen for the single-agent dose expansion, 100 and 250 mg ±LHRH agonist, and an escalation cohort combining 100 mg GDC-9545 with 125 mg palbociclib was enrolled.

GDC-9545 is tolerated well at all dose levels. The most frequently reported adverse events related to GDC-9545 in ≥10% of patients were fatigue (15%), diarrhea and nausea (13%), and arthralgia (11%). Grade ≥3 adverse events were reported in 10 patients (18%), but all were considered unrelated to GDC-9545 by the investigators. Two patients have experienced serious adverse events considered not related to GDC-9545 by the investigator.

In Study GO39932, GDC-9545 was rapidly absorbed with peak concentrations achieved at 1–4 hours (mean time to maximum concentration) after single dose as well as at steady state. The geometric mean half-life after single dose ranged from 26.2–41.4 hours, indicating that once-daily dosing is appropriate for GDC-9545. In general, plasma exposures of GDC-9545 increased with doses at 10, 30, 90, and 250 mg after single and multiple doses. The expansion cohort's exposure was in line with escalation cohort exposure. Pharmacodynamics was assessed by functional imaging with [$_{18}$F]-fluoroestradiol-positron emission tomography and showed robust ER-target engagement across all doses.

Refer to the GDC-9545 Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

GDC-9545 is a potent, orally bioavailable ER-α antagonist and inducer of ER-α degradation that competes with estrogens for binding to the ER with low nanomolar potency; it is being developed for the treatment of women with ER-positive breast cancer.

GDC-9545 demonstrated robust nonclinical activity in ER-positive breast cancer models of *ESR1*-wildtype and *ESR1*-mutation bearing disease. As described in Section 1.2.1.2, GDC-9545 was tolerated in safety pharmacology studies. Specific eligibility criteria

designed to minimize potential risks are included in Section 4.1, and robust safety monitoring and risk mitigation strategies for all expected or potential safety risks are described in Section 5. The implementation of appropriate dose-modification and treatment guidelines, appropriate choice of inclusion/exclusion criteria, real-time safety monitoring and assessments, and periodic assessment of aggregate safety data and benefit–risk ratio combine to form the monitoring and risk mitigation system.

A window of opportunity ("window") study is a type of neoadjuvant study where women with newly diagnosed hormone receptor-positive breast cancer are treated with an experimental drug for 2 weeks prior to surgery. These studies provide access to tumor tissue before, during, and after treatment for PD and correlative studies, providing critical insight into the optimal patient population, differences in activity and mechanisms between agents, influence of the tumor biology on sensitivity, and molecular mechanisms of response or resistance. Window studies are becoming the standard in developing a new drug in hormone receptor–positive breast cancer to inform dose selection and provide early readout on biologic activity.

To ensure consistency with current therapeutic standards, this study requires that definitive surgery take place 15 days (±2 days) after the start of the study treatment. As such, a patient's participation in this study is not expected to delay surgery beyond the standard waiting period. Furthermore, there is no nonclinical, clinical, or mechanistic evidence to suggest that GDC-9545 has a relevant impact on operability or that it increases risks associated with surgery.

Detailed studies in the neoadjuvant setting in prospective randomized clinical trials have demonstrated the utility and validity of changes in Ki67 as a predictor of benefit from of endocrine therapy treatment and of long-term outcome (Dowsett et al. 2005a; Dowsett et al. 2005b; Polychronis et al. 2005; Dowsett et al. 2006; Dowsett et al. 2007; Smith et al. 2007; Ellis et al. 2008; Baselga et al. 2009; Jones et al. 2009) (see Section 3.3.4.1 for additional details).

Although Ki67 measurements in preoperative trials cannot replace the need for adjuvant trials with clinical endpoints, when used along with additional PD data and Phase I dose escalation/expansion safety and efficacy data, they can be highly instructive in selecting the optimal dose for Phase III studies and defining the most appropriate patient populations.

As of November 2018, GDC-9545 has been well-tolerated and shown evidence of activity including in those patients with *ESR1* mutations (see Section 1.2.2). At all doses tested, patients with [^{18}F]-fluoroestradiol positron emission tomography imaging have shown near-complete or complete responses. In addition, there is early indication of ER-pathway reduction by PD markers in the few on-treatment biopsies obtained from the Phase I study.

Overall, there is strong rationale to run a window of opportunity study to select the optimal dose of GDC-9545. In addition, GDC-9545 has a tolerable safety profile that poses minimal risk for patients during treatment and for surgery.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacodynamics, pharmacokinetics, safety and biologic activity of GDC-9545 in patients with Stage I–III operable ER-positive (HER2-negative) untreated breast cancer. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of GDC-9545 when administered in this patient population:

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v.5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results, including ECGs

2.2 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to evaluate the GDC-9545 PK profile on the basis of the following endpoint:

- Plasma concentration of GDC-9545 at steady state

2.3 ACTIVITY OBJECTIVE

The activity objective for this study is to make a preliminary assessment of the activity of GDC-9545 on the basis of the following endpoint:

- Change from baseline in tumor cell proliferation measured by Ki67 expression between pre- and post-treatment samples

2.4 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to GDC-9545 (i.e., predictive biomarkers), can provide evidence of GDC-9545 activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.9) and safety, PK, activity, or other biomarker endpoints
- Cancer-related biomarkers in tumor tissue including DNA mutational status, RNA expression levels, DNA copy number and protein expression
- Modulation of ER and progesterone receptor (PR) protein levels and ER target genes through analysis of paired pre-dose and on-treatment fresh tumor biopsies

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase I, open-label, multicenter, preoperative study to assess changes in Ki67 levels and to evaluate the pharmacodynamics, pharmacokinetics, safety, and biologic activity of GDC-9545 in postmenopausal patients with Stage I–III operable ER-positive (HER2-negative) untreated breast cancer. Approximately 75 patients are expected be enrolled in this study, at approximately 20–30 investigative sites globally.

The study consists of a screening period of up to 28 days; a treatment period of approximately 14 days, including a day for surgery; and a minimum follow-up period of 28 days. Patients will be assigned to one of three treatment cohorts (10, 30, and 100 mg; see Figure 1). GDC-9545 will be administered once daily up to and including the day of surgery (if allowed per local process) on Day 15 (±2 days).

All patients will be required to provide a pretreatment tumor tissue sample. Archival tumor tissue from prior diagnostic formalin-fixed, paraffin-embedded cores (FFPE) may be used; however, if archival tissue is not available or is determined to be unsuitable for required testing, the patient will undergo a tumor biopsy. For the purpose of enrollment, ER, PR, and HER2 will be locally determined prior to beginning of study treatment. Patients who are not evaluable for the primary activity analysis as defined in Section 6 will be replaced.

Surgery will take place on Day 15 (±2). If surgery must be delayed >2 days, the Medical Monitor should be consulted. Surgery should be performed within 24 hours after the last dose of GDC-9545, if possible, to best observe PD knockdown with GDC-9545 in the surgical specimen. In lieu of surgical specimen, a biopsy on Day 14 may be obtained. The surgical specimen is not required if biopsy is obtained on Day 14.

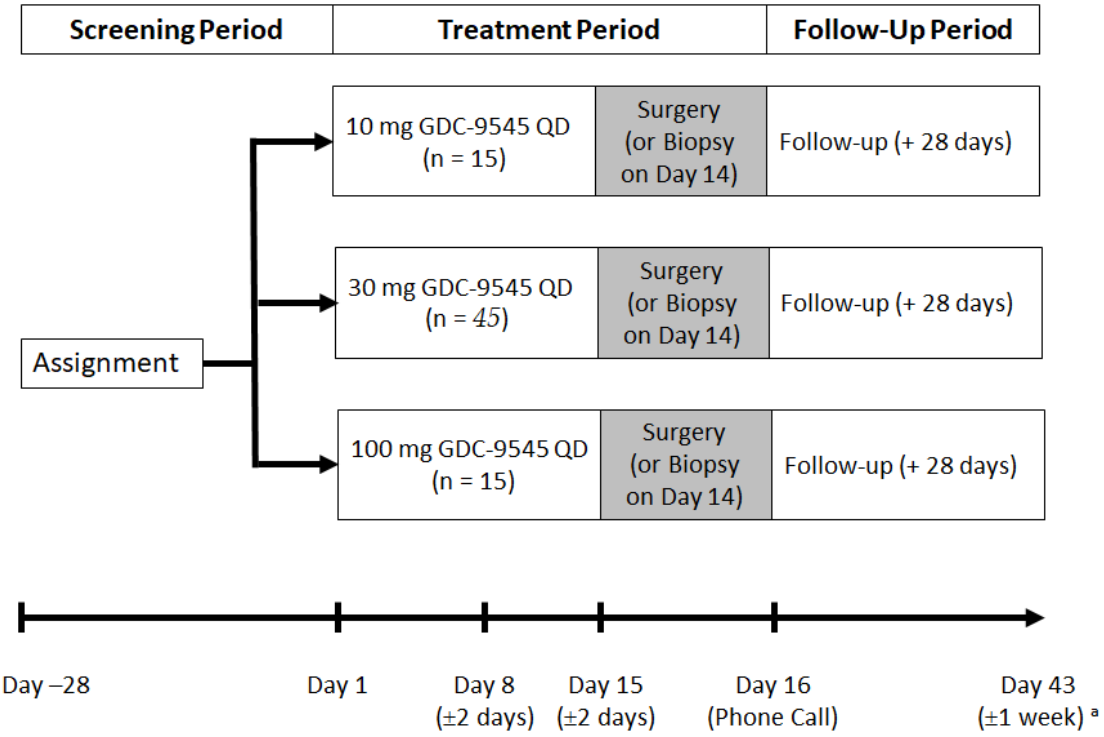
All patients will be closely monitored for adverse events throughout the study and for at least 28 days after the final dose of study treatment (see Section 5.3.1). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). In addition to the safety assessments conducted at scheduled clinic visits, patients will be contacted for a general assessment of adverse events at 24 hours post-surgery by telephone, if applicable.

To assess the steady-state concentrations of GDC-9545, a blood sample will be taken at surgery (see Appendix 1).

If a patient misses more than one dose or the patient's surgery is delayed beyond the allowable window, the Medical Monitor should be consulted about possible replacement.

A schedule of activities is provided in Appendix 1.

Figure 1 Sample Study Schema



QD = once a day

Note: A biopsy on Day 14 may be obtained instead of a surgical specimen. A surgical specimen on Day 15 is not required if biopsy is obtained on Day 14.

[a] *Post-surgery visit should be performed at Day 43 (±1 week) or prior to the initiation of another anti-cancer therapy, whichever occurs first.*

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. The total length of the study, from screening to end of the study, is expected to be approximately *30* months.

In addition, the Sponsor may decide to terminate the study at any time (see Section 4.6.3).

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

Postmenopausal patients with Stage I–III HER2-negative, ER-positive, early stage breast cancer will be enrolled in this study. This patient population is usually treated with surgery followed by anti-hormonal therapy, and/or chemotherapy, according to staging and biological features. Nonclinical studies suggest that ER-positive breast cancer is reliant upon the estrogen pathway giving strong rationale to use an endocrine agent

such as a SERD. Patients with HER2 over-expressing tumors are excluded as these patients would generally be considered for HER2-directed therapy. Given the number of tumor biopsies required as part of this study, the trial will have to be confined to patients with a tumor size of at least 1.5 cm.

3.3.2 Rationale for GDC-9545 Dose and Schedule

GDC-9545 is a potent, orally bioavailable, small-molecule therapeutic agent that is being developed for the treatment of patients with ER-positive breast cancer. Nonclinical anti-tumor activity has been seen in a number of single-agent and combination therapy studies. In addition, early clinical anti-tumor activity has been seen in ER-positive breast cancer. GDC-9545 has demonstrated an acceptable toxicity profile in more than 20 metastatic ER-positive breast cancer patients treated to date. The dose and schedule of GDC-9545 will be orally once daily continuously for 14 days (±2) and the day of surgery (if allowed). GCD-9545 will be administered at 10, 30, and 100 mg.

The doses selected for the Phase I GO40987 study are 10, 30, and 100 mg (rounded from 90 mg to reduce pill burden on patients). These three doses mirror doses studied in the ongoing Phase Ia/b dose-escalation/expansion GO39932 study and that have already cleared the DLT window in the latter study. The traditional safety and efficacy endpoints are being studied in the Phase Ia/b GO39932 study, while the endpoints for the GO40987 study are biomarkers aimed at defining dose-PD and dose-activity relationships to help guide selection of the recommended Phase II dose.

3.3.3 Rationale for PK Sampling Schedule

During the dose escalation of the ongoing Study GO39932, the full PK profile of GDC-9545 has been evaluated as single dose and at steady state at 10, 30, 90, and 250 mg daily. Therefore, only a single PK sample will be taken at steady state to confirm the PK exposure of 10, 30, and 100 mg GDC-9545 in this study.

3.3.4 Rationale for Biomarker Assessments

PD biomarkers will be measured in tissue to determine whether clinically achievable exposures are sufficient for producing the desired effect on the intended molecular target. The evaluation of dose-PD and dose-activity relationships across a range of GDC-9545 doses will enable dose selection.

Breast cancer is a heterogeneous disease (Cancer Genome Atlas Network 2012). Therefore, all patients may not be equally likely to benefit from treatment with GDC-9545. Predictive biomarker samples will be assessed in an effort to identify those patients who are most likely to respond to GDC-9545. PD biomarkers will be assessed to demonstrate evidence of biologic activity of GDC-9545 in patients, to support selection of a recommended dose and dose regimen, and to inform potential revisions to the PK sample collection schedule.

3.3.4.1 Ki67

Ki67 is a well-established proliferation biomarker with prognostic value in ER-positive breast cancer (Anderson et al. 2011). Efficacy of endocrine therapy relies on induction of cell-cycle arrest, and during neoadjuvant treatment, Ki67 levels reflect the ability of endocrine agents to suppress proliferation (Dowsett et al. 2005b; Ellis et al. 2011). There are numerous examples of endocrine agents used in small, short-term neoadjuvant studies whose Ki67 results parallel disease-free recurrence outcomes from large adjuvant studies or PFS in metastatic studies (Guerrero-Zotano and Arteaga 2017).

In the IMPACT trial, short-term changes of Ki67 during the neoadjuvant period of treatment of primary breast cancer with anastrozole or tamoxifen alone or in combination correlated with recurrence-free survival. In this study, Ki67 was assessed at baseline, on Day 15, and at surgery after 12 weeks of treatment (Dowsett et al. 2005a, 2005b). For each treatment arm, the reduction in geometric mean Ki67 levels was significantly higher for anastrozole (76%) than for tamoxifen at both timepoints ($p=0.004$, $p=0.001$, respectively), but no differences were found between tamoxifen (59%) and the combination of anastrozole and tamoxifen (64%). These results mirrored the statistically significant ($p=0.004$) recurrence-free survival outcome difference between anastrozole and tamoxifen (4.3% at 10 years) in the much larger adjuvant ATAC trial ($n=9366$) without the requirement of a long follow-up. In addition, after a median follow-up of 68 months, anastrozole significantly prolonged disease-free survival (575 events with anastrozole vs. 651 with tamoxifen; HR=0.87; 95% CI: 0.78, 0.97; $p=0.01$) and time-to-recurrence (402 vs. 498; HR=0.79; CI: 0.70, 0.90; $p=0.0005$), and significantly reduced distant metastases (324 vs. 375; HR=0.86; CI: 0.74, 0.99; $p=0.04$) and contralateral breast cancers (35 vs. 59; 42% reduction, CI: 12%, 62%; $p=0.01$) (Baum et al. 2002; Howell et al. 2005; Forbes et al. 2008)

The POETIC trial, a Phase III randomized clinical trial with approximately 4000 patients with early breast cancer, prospectively tested whether short-term perioperative endocrine therapy with an AI followed by standard adjuvant therapy can improve outcome in postmenopausal women with ER-positive breast cancer, whether the proliferation marker Ki67 as measured by immunohistochemistry after 2 weeks of AI therapy will predict for recurrence-free survival and whether molecular profiling 2 weeks after starting endocrine therapy predicts better for long-term outcome than at diagnosis. Similar to the IMPACT study, an early evaluation of Ki67 levels after 2 weeks of

treatment were shown to correlate to 5-year recurrence rate (low Ki67 8.5% 5-year TTR, high Ki67 19.6% 5-year TTR) (Robertson et al. 2018).

The neoadjuvant NEWEST study helped establish the optimal dose of the ER antagonist fulvestrant (500 mg) on the basis of significantly greater suppression of Ki67 compared with the lower dose of 250 mg after 4 weeks of treatment ($p < 0.0001$) (Kuter et al. 2012). Fulvestrant at 500 mg had a mean percent change from baseline of 78% at 4 weeks and 77% at 16 weeks. Fulvestrant at 250 mg had a mean percent change from baseline of 47% at 4 weeks and 63% at 16 weeks. These early Ki67 differences mirrored the results of the Phase III CONFIRM trial in advanced breast cancer, which also showed superiority of the 500-mg dose over the 250-mg dose (CBR in patients with measurable disease 45.6% versus 39.6% and PFS 6.5 months versus 5.4 months) (Di Leo et al. 2010).

In summary, reduction in Ki67 after neoadjuvant treatment with AIs and fulvestrant is a good marker of suppression of cellular proliferation, correlates with long-term efficacy outcomes, and mirrors results of large adjuvant or metastatic endocrine trials, which make it an attractive endpoint to assess in the present trial.

3.3.4.2 Pharmacodynamic Pathway Modulation

Pre- and on-study tumor biopsies from the same lesion will be collected to assess ER protein degradation and PR protein levels. Similar to Ki67, reduction of both ER and PR were significantly greater with the 500-mg dose of fulvestrant than the 250-mg dose after 4 weeks of treatment in the NEWEST study (ER 50% vs. 14%, $p < 0.0001$, PR 81% vs. 46%, $p = 0.0018$) (Kuter et al. 2012). In addition, paired tumor biopsies will enable assessment of ER pathway suppression using RNA analysis of ER target genes.

3.3.4.3 Plasma Samples for Somatic Tumor Mutation Analysis

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). Recent nonclinical and clinical data suggest that mutations in *ESR1* and *PIK3CA* are associated with endocrine-resistant breast cancer (Shou et al. 2004; Miller et al. 2010; Robinson et al. 2013; Toy et al. 2013; Jeselsohn et al. 2014; Bosch et al. 2015). To gain insights into potential causal relationships between the clinical activity of GDC-9545 and resistance mechanisms, genes related to PI3K signaling and endocrine resistance as well as reported and unreported chromosomal alterations resulting from the tumorigenesis process may be assessed in circulating-tumor DNA (ctDNA) isolated from plasma using digital polymerase chain reaction, and/or targeted next-generation sequencing (NGS).

3.3.4.4 Tumor Samples for Somatic Mutation Analysis

NGS techniques such as exome sequencing may offer a unique opportunity to identify biomarkers of response and/or resistance to GDC-9545. For example, genes related to PI3K signaling and endocrine resistance as well as reported and unreported chromosomal alterations resulting from the tumorigenesis process may be assessed.

3.3.4.5 Blood Sample for Next-Generation Sequencing

NGS technologies generate a large quantity of sequencing data. Tumor DNA can contain both reported and unreported chromosomal alterations because of the tumorigenesis process. To help control for sequencing calls in previously unreported genomic alterations, a predose blood sample will be taken to determine whether the alteration is somatic using targeted NGS.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 75 postmenopausal women with HER2-negative, ER-positive, Stage I–III operable untreated breast cancer will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Women age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor ≥ 1.5 cm in largest diameter by ultrasound
  - Stage I–III operable breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease [e.g., large tumors, clinically positive axillary lymph nodes] signs and symptoms)
- ER-positive tumor and HER2-negative breast cancer as per local laboratory testing
- Postmenopausal status defined as one of the following:
  - Prior bilateral surgical oophorectomy
  - Age ≥ 60 years
  - Age < 60 years and amenorrhea 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and estradiol levels and follicle-stimulating hormone (FSH) levels in the postmenopausal range
- Breast cancer eligible for primary surgery

- Submission of a representative tumor tissue specimen

  A FFPE tumor specimen in a paraffin block (preferred) or *approximately* 15 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If less than 12 slides are available, the patient may still be eligible for the study after Medical Monitor approval has been obtained. Confirmation of *available tissue sample* is required prior to Day 1 of treatment. If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, tumor tissue must be obtained from a biopsy performed at screening. A biopsy may also be performed at screening if a patient's archival tissue test results do not meet eligibility criteria. Refer to Section 4.5.9 for additional information on tumor specimens collected at screening.
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1
- Adequate organ function as defined by the following criteria:
  - ANC $\geq 1500/\mu L$
  - Platelets $\geq 100{,}000/\mu L$
  - AST and serum ALT $\leq 3 \times$ upper limit of normal (ULN)
  - Total serum bilirubin $\leq 1.5 \times$ ULN

    Inclusion of patients with increased serum indirect bilirubin ($\leq 3 \times$ ULN) due to Gilbert's syndrome is permitted.
  - Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate ≥ 50 mL/min/1.73 m^2 (Michels et al. 2010)

4.1.2 Exclusion Criteria

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

- Diagnosis of inflammatory breast cancer
- Diagnosis of bilateral breast cancer
- Concurrent use of hormone replacement therapies
- Previous systemic or local treatment for the primary breast cancer currently under investigation (including surgery, radiotherapy, cytotoxic and endocrine treatments)
- Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to study entry
- Current treatment with any systemic anti-cancer therapies
- Major surgery within 4 weeks prior to enrollment
- Radiation therapy within 2 weeks prior to enrollment
- Diagnosis of any secondary malignancy within 3 years prior to enrollment, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
- Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or upper gastrointestinal (GI) surgery including gastric resection

- Known HIV infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., hepatitis B or hepatitis C virus), current alcohol abuse, or cirrhosis
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
- History of allergy to GDC-9545 or any of its excipients
- Any condition requiring anticoagulants, such as warfarin, heparin, or thrombolytic drugs
- History of documented hemorrhagic diathesis or coagulopathy
- History or presence of symptomatic bradycardia
- Baseline heart rate $\leq$55 bpm prior to enrollment
- History or presence of sick sinus syndrome
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction
- QT interval corrected through use of Fridericia's formula (QTcF) $>$470 ms demonstrated by at least two ECGs $>$30 minutes apart
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval
- History or presence of uncontrolled hypothyroidism
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

4.2 METHOD OF TREATMENT ASSIGNMENT

Treatment assignment will be conducted using an interactive voice or web-based response system (IxRS). After written informed consent has been obtained, all patients will receive a screening number, which will be assigned by the IxRS. Following completion of the screening period and after all patient eligibility requirements are

confirmed, patients will be assigned to a cohort and given an identification number (a different number from the screening number) by the IxRS.

Patients will be assigned to one of three treatment arms based on the following stratification factors:

- Tumor grade (1 and 2 vs. 3)
- Nodal status (cytologically positive vs. radiologically or cytologically negative).

  If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then fine-needle aspiration (FNA) or core biopsy is required to confirm nodal status.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is GDC-9545.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 GDC-9545

GDC-9545 will be supplied by the Sponsor and will be provided in two different strengths, 10-mg and 50-mg tablets, packaged in high-density polyethylene bottles with a plastic child-resistant cap with induction seal and desiccant. For information on the formulation and handling of GDC-9545, see the pharmacy manual and the GDC-9545 Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimen is summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on storage and administration.

The research staff at each participating site will provide detailed instructions and training for the handling of GDC-9545 and its administration to each patient at the beginning of their study participation. Patients will be instructed to complete a daily medication diary.

Patients will be asked to return any remaining study drug from the previous dosing days as well as all used and unused tablet containers and medication diary.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of GDC-9545 overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

The full prescribed dose of GDC-9545 should be taken by mouth in the morning, at approximately the same time each day unless otherwise specified. GDC-9545 may be taken with or without food.

GDC-9545 will be administered once daily continuing up to and including the day of surgery. Patients are allowed to take their final dose of GDC-9545 in the morning on the day of surgery if allowed per local process. If surgery must be delayed >2 days, the Medical Monitor should be consulted. Continuous dosing will begin on Day 1. On Day 1, GDC-9545 will be administered in the clinic. All other doses of GDC-9545 will be administered on an outpatient basis.

For missed doses, patients should just take the next scheduled dose, without compensating for the missed dose. If a patient misses more than one dose, the Medical Monitor should be consulted about possible replacement, if applicable.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (GDC-9545) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Continued Access to GDC-9545

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide the Genentech IMP GDC-9545 or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing GDC-9545 in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to screening through 4 weeks following final dose of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Symptomatic anti-emetics, anti-diarrheal therapy, may be administered at the investigator's discretion. All concomitant medication and/or therapies should be documented in the patient's eCRF.
- Bone-sparing agents (e.g., bisphosphonates, denosumab for the treatment of osteoporosis/osteopenia are allowed in the study provided patients were on stable doses for at least 4 weeks prior to enrollment.

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

As a perpetrator of DDIs, GDC-9545 has been shown to have the potential to inhibit and activate human CYP3A4/5 enzymes in vitro. As a victim, GDC-9545 is primarily glucuronidated via UGT1A4 with minor contributions from CYP3A4 and 2C9 enzymes. Low potential for clinically relevant DDI is anticipated for GDC-9545 both as a perpetrator and as a victim. Although the potential for clinically significant DDI as a victim or perpetrator is anticipated to be low to moderate based on the physiologically-based pharmacokinetic simulations, caution should be taken with the coadministration of drugs with narrow therapeutic index (see the GDC-9545 Investigator's Brochure).

4.4.2.2 Medications Given with Precaution due to Effects Related to Decreases in Heart Rate

Caution should be taken with the coadministration of drugs known to cause decreases in heart rate (see Section 5.1.1.7).

4.4.2.3 Herbal Therapies

Herbal therapies, except phytoestrogen-containing herbal therapies, not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

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

Hormone replacement therapy, selective ER modulators (e.g., raloxifene), and phytoestrogen-containing herbal therapies are prohibited

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for any adverse events prior to Day 1; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. Laboratory tests collected within 72 hours of Day 1 and deemed acceptable by the investigator may be used to proceed with dosing on Day 1. Laboratory tests must be collected prior to dosing on Day 1. In addition to the safety assessments conducted at scheduled clinic visits, patients will be contacted for a general assessment of adverse events at 24 hours post-surgery by telephone, if applicable.

4.5.1 Informed Consent Forms and Screening Log

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

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, breast cancer history (including tumor size, tumor grade, nodal status and PR status), and reproductive status, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal,

genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

A limited, symptom-directed physical examinations should be performed at the post-surgery visit and will include an assessment of the surgery wound. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate, systolic and diastolic blood pressure (while the patient is in a seated position), and temperature *(per institutional practice)*. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status scale will be assessed at screening and per Appendix 4.

4.5.6 Tumor Evaluations

Bilateral breast ultrasounds will be obtained per institutional guidelines within 28 days prior to enrollment. Ultrasounds performed prior to surgery may be unilateral or bilateral at the discretion of the investigator. If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then FNA or core biopsy is required. Sonographic tumor measurements are to be recorded in the eCRF. The tumor site may be marked with a radiopaque clip or marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy.

4.5.7 Biological Response Assessment.

The biological response to the study treatment will be assessed by measuring changes in cell proliferation (Ki67 expression) using FFPE histopathology sections of the tumor biopsy specimens taken at baseline and at day of surgery.

4.5.8 Surgical Treatment Plan

The planned and actual surgical treatment (breast-conserving surgery or mastectomy) performed should be documented and reported in the eCRF. Patients should be reassessed after completion of GDC-9545 administration and prior to surgery.

4.5.9 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, magnesium, AST, ALT, total and direct bilirubin, and ALP
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination if clinically indicated (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- FSH; for patients $<$60 years
- Estradiol; for patients $<$60 years
- Coagulation (PT. aPTT, and INR)

The following samples will be sent to the Sponsor or a designee for analysis:

- Plasma samples for PK analysis
- Blood samples for analysis of ctDNA and plasma biomarkers
- Blood samples for NGS
- Archival (diagnostic) or newly collected tumor tissue sample obtained prior to initiation of treatment

  A representative FFPE tumor specimen in a paraffin block (preferred) or $approximately$ 15 unstained, serial sections, (freshly cut) must be submitted along with an associated pathology report. Confirmation of $available\ tissue$ sample is required prior to enrollment. If less than 15 slides are available, the patient may still be eligible for the study after Medical Monitor approval has been obtained.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples should contain a minimum of 500 viable tumor cells per section that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least two cores, three preferable, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. FNA (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

  If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required (at least three cores).

- An FFPE tumor block from surgical resection or tissue sample obtained on Day 14 is required. If a tumor block cannot be submitted for various reasons (e.g., the tumor tissue is not sufficient at surgical resection or due to site restrictions), approximately 15 unstained slides from the surgical specimen are required. The surgical specimen is not required if biopsy is obtained on Day 14.

Exploratory biomarker research using blood, plasma, and tissue samples may include, but will not be limited to, protein-based analyses, copy number and mutational analysis of cancer-related genes, gene expression of ER target genes and signatures associated with breast cancer subtypes, immune-related and PI3K signaling, and analysis of ctDNA. Exploratory biomarker research may involve extraction of DNA, ctDNA, or RNA; analysis of somatic mutations and chromosomal alterations; and use of NGS.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11, biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma samples collected for PK analysis may be needed for additional exploratory research, such as PK or PD assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, and tumor tissue samples collected for biomarker research will be destroyed no later than 15 years after the final Clinical Study Report has been completed or earlier depending on local regulations
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis including data on mutations will be subject to the confidentiality standards described in Section 8.4.

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.

4.5.10 Electrocardiograms

Triplicate ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1). ECGs acquired on different days should be as closely time-matched as feasible. Three interpretable ECG recordings (e.g., without artifacts) must be obtained at each timepoint (±5 minutes). The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Single ECG recordings may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is >500 ms and/or 60 ms longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and triplicate ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 5.1.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval [see Appendix 2 and Appendix 3], severe bradycardia).

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples 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.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- 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

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to GDC-9545, diseases, or drug safety:

- Leftover blood, plasma, and FFPE tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a

comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples 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.

Given the complexity and exploratory nature of the analyses of RBR samples, 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.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

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

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time

and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Adverse event that, in the investigator's or surgeon's opinion, has the potential to delay surgery
- Any other adverse event that cannot be adequately managed
- Protocol violation requiring discontinuation of study treatment
- Patient is not compliant with study procedures
- Patient is lost to follow-up

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will be replaced.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor
- Adverse event
- Loss to follow-up

Every effort should be made to obtain a reason for patient discontinuation from the study but have not withdrawn consent. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will be replaced.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

GDC-9545 is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on the anticipated mechanism of action, nonclinical data (in vitro and in vivo), published data on similar molecules, and clinical experience with GDC-9545. The anticipated important safety risks for GDC-9545 are outlined below. Please refer to the GDC-9545 Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1.2). Patients will undergo real-time safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Potential Risks Associated with GDC-9545

5.1.1.1 Hepatotoxicity

Dose-dependent hepatic effects were observed in repeat-dose studies in both rats and monkeys given GDC-9545. Microscopic changes and liver enzyme elevations were observed. Changes were reversible at all dose levels assessed. Please refer to the GDC-9545 Investigator's Brochure for further information.

Liver enzyme elevation has been reported in association with some oral SERD molecules currently in early development (see GDC-9545 Investigator's Brochure for further information). Changes in liver enzymes have been reported with the oral selective estrogen receptor modulator (SERM) tamoxifen (reported as common, ≥1% to <10%) and the injectable SERD fulvestrant (reported as very common, ≥10%) (eMC 2016a; 2016b). Hepatitis, hepatic failure and hepatic necrosis are reported as rare (≥ 0.01% and < 0.1%) in patients receiving tamoxifen. Hepatic failure and hepatitis are reported as uncommon (≥ 1/1000 to < 1/100) in patients receiving fulvestrant.

Guidelines for management of patients who develop hepatotoxicity are provided in Table 1.

5.1.1.2 Gastrointestinal Toxicities (Nausea, Vomiting, Diarrhea)

During repeat-dose testing of GDC-9545 with monkeys, vomiting, diarrhea, and soft stools were reported. Please refer to the GDC-9545 Investigator's Brochure for further information.

GI toxicities have been reported in association with some oral SERD molecules currently in early development (see GDC-9545 Investigator's Brochure for further information). The mechanism of action of SERD associated GI toxicities is not clear and without randomized data, it is impossible to be sure if there is a true treatment effect. However, patients should be closely monitored for GI effects and any consequent sequelae such as changes in blood chemistry parameters or dehydration.

Guidelines for management of patients who develop GI toxicities are provided in Table 1.

5.1.1.3 Thromboembolic Events

No evidence of thrombosis, bleeding events, or wound closure issues were seen in nonclinical studies in rats and monkeys given GDC-9545.

Thromboembolic events may occur in patients with malignancies. Against this background of malignancy, they are reported to occur commonly in patients receiving fulvestrant (≥1/100 to <1/10) (eMC 2016a). There are no randomized placebo controlled data from oral SERD programs at present.

The SERM tamoxifen is reported to carry a 2- to 3-fold increased risk of thromboembolic events in the adjuvant setting (eMC 2016b).

To date, no patients treated with GDC-9545 in ongoing Phase I Study GO39932 have experienced any thromboembolic events or issues with wound healing. However, given limited data, high-risk patients (e.g., patients with a history of bleeding diathesis, coagulopathy, low platelet counts, or need for long-term anticoagulant therapy) are excluded from this study to minimize unexpected risk to patients (see Section 4.1.2).

Guidelines for management of patients who develop thromboembolic toxicities are provided in Table 1.

5.1.1.4 Renal Dysfunction

Dose-dependent effects on the kidneys were observed in repeat-dose studies in both rats and monkeys given GDC-9545. Microscopic findings consistent with renal injury were observed along with mild increases in creatinine, urea, and phosphorus. Some findings were reversible during the recovery phase in monkeys at the recovery dose assessed, but no reversibility was observed in rats. Please refer to the GDC-9545 Investigator's Brochure for further information.

Renal failure or acute kidney injury are not listed as unwanted effects of fulvestrant (eMC 2016a).

Renal function tests will be closely monitored in GDC-9545 studies with serum creatinine and BUN measurements.

Guidelines for management of patients with renal dysfunction are provided in Table 1.

5.1.1.5 Changes in Female Reproductive Organs and Menopausal Symptoms

GDC-9545-related effects in reproductive tissues consistent with expected pharmacology of GDC-9545 on ER degradation were observed at all doses in rats and monkeys in repeat-dose toxicity studies. Changes observed included ovarian follicular cysts (including intracystic hemorrhage), decreased uterine weight, cervical and vaginal epithelial atrophy, and decreased pituitary gland weight. Changes were partially reversible in monkeys and not reversible in rats during the follow-up period possibly due to the presence of pharmacologically active exposures of GDC-9545 at the end of the 28-day recovery period. Please refer to the GDC-9545 Investigator's Brochure for further information.

Based on the anti-estrogenic pharmacological activity of GDC-9545, its effects are anticipated to be similar to, but potentially more severe than, those of normal menopause, such as loss of muscle and bone, hot flashes, vaginal dryness or discharge, irritation, mood swings, and decreased libido.

Hot flushes and vaginal discharge have been reported in association with oral SERD molecules currently in early development. Please refer to the GDC-9545 Investigator's Brochure for further information.

Unlike GDC-9545, the SERM tamoxifen promotes the growth of endometrial tissue in vitro, acting as an agonist of ER in that tissue (Hu et al. 2015). Endometrial changes including polyps ($\geq 1\%$ and $< 10\%$) and endometrial cancer (uncommon, $\geq 0.1\%$ and $< 1\%$) are listed as undesirable effects of tamoxifen. GDC-9545 and fulvestrant (both SERDs) are not agonistic in endometrial cells. The effects of GDC-9545 in human endometrial tissue are unknown, but endometrial agonism is not anticipated.

Changes in reproductive organs and menopausal symptoms should be managed according to local standards of care.

It is recommended that a specialist gynecological opinion be sought in the event of any abnormal bleeding from the reproductive tract.

5.1.1.6 Female Infertility

GDC-9545 has not been tested in male animals. Perturbation and arrest of the estrus cycle was observed microscopically in both female rats and monkeys. This was not reversible during the follow-up period.

It is unknown whether a longer recovery period in animals would reveal whether the observed perturbation in the estrus cycle is reversible. While this finding remains incompletely explained pending further study with a longer recovery period, any patients with concerns for future fertility should be made aware of this potential issue prior to coming onto this study. Their concerns, including fertility preservation, should be discussed prior to enrolling into any study with GDC-9545. Please refer to the GDC-9545 Investigator's Brochure for further information.

5.1.1.7 Bradycardia

During the nonclinical 4-week toxicity study in cynomolgus monkeys, GDC-9545 related reductions in heart rate or increases in RR interval were observed (surface and telemetry leads) on Day 13 at 20, 60, and 200 mg/kg and on Day 23 at 60 mg/kg. These changes were considered related to GDC-9545 but were within the normal range for cynomolgus monkey and not considered adverse.

At the time of the completion of the dose escalation portion of Study GO39932, three patients (10%) in the 90 mg cohort, had reported Grade 1 asymptomatic bradycardia. Upon further review of clinical safety data (vital signs/ECGs) patients at all dose levels were noted to have decreased heart rate from baseline and/or Grade 1 bradycardia. In all patients, bradycardia/decreased heart rate was not accompanied with clinically significant ECG changes or exercise intolerance.

Until there is a clear understanding of the clinical profile of bradycardia with GDC-9545, ECGs will continue to be collected during the study. Caution should be taken with the coadministration of drugs known to cause decreases in heart rate.

Guidelines for management of patients who develop bradycardia are provided in Table 1.

5.1.1.8 Drug–Drug Interactions

Please refer to the Section 4.4.2.1 for the potential DDI risks and the recommendations of the concomitant medications and foods.

5.1.2 Management of Patients Who Experience Adverse Events

If, in the investigator's or surgeon's opinion, an adverse event has the potential to delay surgery, GDC-9545 treatment should be discontinued and the patient withdrawn from the study (see Section 4.6.1). Patients who discontinue study treatment prematurely will be replaced.

5.1.2.1 Dose Modifications

There will be no dose reductions allowed for GDC-9545. GDC-9545 may be held or discontinued per Section 5.1.2.3.

5.1.2.2 Treatment Interruption

GDC-9545 treatment may be temporarily suspended as appropriate for managing of toxicity considered to be related to study drug. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

If a patient misses more than one dose, the Medical Monitor should be consulted about possible replacement of the patient.

5.1.2.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 1. Additional guidelines are provided in the subsections below.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Elevation of hepatic transaminases	• Patients presenting with jaundice, coagulopathy, abdominal pain, or other symptoms suggestive of hepatic pathology should have their liver function tests checked and imaging of the liver performed. If the liver enzymes are elevated with no obvious malignant cause found, a hepatologist should be consulted. • Patients experiencing hepatic enzyme elevation should be treated and managed per standard of care. • Discontinue GDC-9545 for Grade ≥ 3 events and consult with the Medical Monitor.
Gastrointestinal toxicities (nausea, vomiting, diarrhea)	• Monitor patients closely for GI symptoms and the effects on their well-being. Patients experiencing nausea, vomiting, and diarrhea should be managed according to local standards of care, including use of anti-diarrheal agents and appropriate supportive care including hydration and dietary modification as appropriate. Infectious or alternate etiology should be excluded. • Discontinue GDC-9545 for Grade ≥ 3 events and consult with the Medical Monitor.
Venous thromboembolic events including pulmonary embolism	• Patients should be advised to seek immediate medical attention if they become aware of any symptoms of pulmonary embolism or DVT, such as acute onset of chest pain, shortness of breath, or swelling in extremities. • Manage and treat patients according to local standards of care (e.g., consider anti-coagulation and/or IVC filter). • Discontinue GDC-9545 for related VTE or pulmonary embolism and consult with the Medical Monitor.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Renal toxicity (decrease in post-treatment GFR of > 25% potentially attributed to GDC-9545)	• Patients experiencing deterioration in renal function should be treated and managed according to local standard of care. • Discontinue GDC-9545 and consult with the Medical Monitor.
Bradycardia	• Monitor patients closely for symptomatic bradycardia that may have effects on their well-being. • Patients experiencing symptomatic bradycardia should be treated and managed per standard of care. • For Grade 2 bradycardia, withhold GDC-9545 and consult with the Medical Monitor. GDC-9545 is not to be resumed without permission from the Medical Monitor. • For Grade ≥ 3 bradycardia, discontinue GDC-9545 and consult with the Medical Monitor.
Grade ≥ 3 adverse events potentially attributed to GDC-9545	• Discontinue GDC-9545 and consult with the Medical Monitor.

DVT = deep vein thrombosis; GFR = glomerular filtration rate; GI = gastrointestinal; IVC = inferior vena cava; PE = pulmonary embolism; ULN = upper limit of normal; VTE = venous thromboembolic events.

5.1.2.4 Management of Increases in QT Interval

Study drug should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value
- Sustained absolute QTcF that is > 515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT

interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 and 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Grade $\geq$3 nausea/vomiting/diarrhea
- Grade $\geq$2 thromboembolic events (pulmonary embolism, deep vein thrombosis, and embolism
- Grade $\geq$3 Renal failure (including acute kidney injury or other similar medical concepts)
- Grade $\geq$3 hepatitis or elevation in ALT or AST
- Grade $\geq$2 vaginal or uterine hemorrhage
- Grade $\geq$2 bradycardia
- Any Grade of endometrial cancer
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)

- Suspected transmission of an infectious agent by the study drug, as defined below:

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.1.2 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 5.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

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

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

Table 3 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

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

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

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

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Breast Cancer

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

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

- Planned hospitalization required by the protocol for breast cancer surgery
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

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

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

5.3.5.11 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For GDC-9545, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with GDC-9545, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], *M.D., M.P.H.* (Primary)
Telephone Nos.: [redacted] Mobile; [redacted]
(Office; [redacted])

Alternate Medical Monitor contact information for all sites:

PPD Medical Monitor:

North America
Email : rtpsafety@ppdi.com
Telephone: (888) 483-7729

EMEA and Asia Pacific:
Email : emeaasiasafetycentral.sm@ppdi.com
Telephone: (44) 1223-374-240

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

North America:
Fax : (888) 529-3580
Email : rtpsafety@ppdi.com
Telephone: (888) 483-7729 (if site cannot report via fax)

EMEA and Asia Pacific:
Fax : 44.1223.374.102
Email : emeaasiasafetycentral.sm@ppdi.com
Telephone: 44.1223.374.240 (if site cannot report via fax)

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

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

the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 28 days after the final dose of study treatment are provided in Section 5.6.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided in Section 5.4.2.1.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- GDC-9545 Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final analysis will be performed after LPLV and subsequent data cleaning. The safety analysis will be based on the safety-evaluable population, and activity analysis will be based on the patients who completed study treatment. All summaries will be presented according to the assigned dose level and cohort. In general, data will be summarized as warranted, and listings will be used in place of tables when the samples sizes are small. Continuous variables will be summarized using means, standard deviations, median, and ranges; categorical variables will be summarized using counts and percentages.

6.1 DETERMINATION OF SAMPLE SIZE

This study is intended to obtain preliminary safety, PK, PD, and activity information. The sample sizes do not reflect any explicit power and type I error considerations.

The range of mean Ki67 expression changes are from 66% (Opportune) to 76% (IMPACT) for 2-week treatment (see Section 3.3.4.1). The planned enrollment for this study is approximately *75* patients. *At least* 15 patients per cohort will provide a more robust safety profile as well as sample size for preliminary assessment of activity based on Ki67 expression. In Table 4, two-sided 80% CIs for Ki67 expression changes are listed, based on different assumed observed changes. The CIs show clear shift pattern at the sample size of 15 patients. *To better evaluate the Ki67 expression change at 30 mg, the sample size is increased to 45. The 80% CIs show clear separation at this patient sample size.*

Table 4 Two-Sided 80% Confidence Intervals for Ki67 Expression Change

	Assumed Observed Change			
Sample size	60%	70%	80%	90%
15	(53.9%, 66.8%)	(62.9%, 77.9%)	(71.9%, 89.0%)	(80.9%, 100%)
20	(54.7%, 65.8%)	63.8%, 76.8%)	(72.9%, 87.8%)	(82.0%, 98.7%)
45	*(56.4%, 63.8%)*	*(65.8%, 74.5%)*	*(75.2%, 85.1%)*	*(84.6%, 95.7%)*

6.2 SUMMARIES OF CONDUCT OF STUDY

Summaries of study conduct will include all enrolled patients in the study. The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for discontinuations and premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including, but not limited, to age, race/ethnicity, weight, type of malignancy, duration of malignancy, and baseline ECOG Performance Status) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by dose level.

6.4 SAFETY ANALYSES

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

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

Safety will be assessed through summaries of adverse events, changes in laboratory test results (including ECGs), changes in vital signs, and GDC-9545 exposure.
All adverse events occurring on or after treatment on Day 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v5.0 toxicity grade.
Relevant laboratory and vital sign (pulse rate, blood pressure, and temperature) data will be displayed by time, with NCI CTCAE v5.0 Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized by NCI CTCAE v5.0.

Safety data will be accumulated up to the end of the patient's follow-up period.

6.5 PHARMACOKINETIC ANALYSES

The sparse PK concentration data at the steady state will be summarized by dose level and compared with the historical PK profiles from the Phase I study.

Additional PK analyses may be conducted as appropriate.

6.6 ACTIVITY ANALYSES

The activity analysis population will consist of all patients who completed study treatment and who have tumor biopsy specimens available at baseline and at surgery for assessment of activity.

The activity is defined as change from baseline in tumor cell proliferation measured by Ki67 expression between pre- and post-treatment samples. The activity will be summarized by dose level.

On the assumption of a log normal distribution, Ki67 values will be log transformed before analysis. Log(Ki67post) and log(Ki67pre) will be used to denote the mean of the logs of the post-treatment and pre-treatment values, respectively. A value of 0.1 will be added to every untransformed Ki67 value to avoid the mathematical anomaly that arises because the log of zero is minus infinity. The result of mean log changes and CI can be calculated and displayed on their original scale by back transformation.

6.7 BIOMARKER ANALYSES

Exploratory biomarker analyses may be performed in an effort to understand the association of these markers with study treatment response. The biomarker analysis will be descriptive in nature includes modulation of ER-target genes as well as ER and PR protein levels.

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor 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.

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 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 applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for

Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national law.

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the 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 and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

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 national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, 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.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

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 the Sponsor and to the IRB/EC in accordance with established IRB/EC

policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, a member of the Roche Group. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 20–30 sites globally will participate to enroll approximately *75* patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for more details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving

an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

	Screening	In–Clinic Treatment		Surgery [a]	Post-Surgery Visit [k]
Day (Window)	(Day –28 to Day –1)	1	8 (±2)	15 (±2)	43 (±1 week)
Informed consent (Section 4.5.1) [b]	x				
Medical history, demographic data and baseline conditions (Section 4.5.2)	x				
Physical examination (Section 4.5.3)	x				x [c]
Height	x				
Weight	x				
Vital signs (Section 4.5.4)	x	x	x	x	x
ECOG performance status (Section 4.5.5)	x	x		x	x
Hematology (Section 4.5.9)	x [d]	x [d]	x	x	
Chemistry (Section 4.5.9)	x [d]	x [d]	x	x	
Coagulation (PT, aPTT, and INR) (Section 4.5.9)	x [d]	x [d]	x	x	x
FSH (Section 4.5.9) [e]	x				
Estradiol (Section 4.5.9) [e]	x				
Triplicate 12-lead ECG (Section 4.5.10)	x	x	x [f]	x [f]	
Tumor evaluation (Section 4.5.6)	x				
Tumor tissue (Section 4.5.9)	x			x or biopsy on Day 14	
Confirmation of *available* tissue sample	x				
Urinalysis (Section 4.5.9)	x				

Appendix 1: Schedule of Activities

	Screening	In–Clinic Treatment		Surgery [a]	Post-Surgery Visit [k]
Day (Window)	(Day −28 to Day −1)	1	8 (±2)	15 (±2)	43 (±1 week)
Plasma PK sample (Section 4.5.9) [g]				x or prior to biopsy on Day 14	
Blood sample for biomarkers (ctDNA) (Section 4.5.9)		x [d]		x or prior to biopsy on Day 14	x
Blood sample for biomarkers (NGS) (Section 4.5.9)		x [d]			
Study drug compliance [h]		x	x	x	
GDC-9545 dosing (Section 4.3.2) [i]		x		x	
Adverse events	x	x	x	x [j]	x
Concomitant medication	x	x	x	x	x

ctDNA = circulating-tumor DNA; ECOG = Eastern Cooperative Oncology Group; FSH = follicle-stimulating hormone; NGS = next-generation sequencing; PK = pharmacokinetic.

[a] If surgery must be delayed > 2 days, the Medical Monitor should be consulted.

[b] Signed informed consent must be provided prior to any study-specific evaluations.

[c] A limited, symptom-directed physical examinations should be performed at the post-surgery visit and will include an assessment of the surgery wound.

[d] Laboratory tests must be collected prior to dosing and preferably within 72 hours of Day 1.

[e] For patients < 60 years only.

[f] ECG should be performed if clinically indicated.

[g] *A single blood sample* for PK needs to be collected prior to surgery or on Day 14 if biopsy obtained, and as close as possible to post-treatment biopsy collection. The PK collection time and the dose administration time prior to PK collection should be recorded.

[h] Patients will receive and should be instructed to complete a medication diary (see Section 4.3.2). The medication diary and unused drug and bottles of GDC-9545 should be collected and reviewed on Day 8 and at the surgery visit for drug accountability.

[i] GDC-9545 will be orally self-administered on Days 1−14 (±2 days).

[j] Assessment of adverse events will also be done at 24 hours post-surgery (±1 day) by telephone contact, if applicable.

[k] *Post-surgery visit should be performed at Day 43(± 1 week) or prior to the initiation of another anti-cancer therapy, whichever occurs first.*

Appendix 2
Drugs with Known Torsades de Pointes Risk

Information available at www.azcert.org.

Amiodarone	Gatifloxacin	Sotalol
Anagrelide	Grepafloxacin	Sparfloxacin
Arsenic trioxide	Halofantrine	Sulpiride
Astemizole	Haloperidol	Sultopride
Azithromycin	Ibogaine	Terfenadine
Bepridil	Ibutilide	Terlipressin
Chloroquine	Levofloxacin	Terodiline
Chlorpromazine	Levomepromazine	Thioridazine
Cilostazol	Levomethadyl acetate	Vandetanib
Ciprofloxacin	Levosulpiride	
Cisapride	Mesoridazine	
Citalopram	Methadone	
Clarithromycin	Moxifloxacin	
Cocaine	Ondansetron	
Disopyramide	Oxaliplatin	
Dofetilide	Papaverine HCl	
Domperidone	Pentamidine	
Donepezil	Pimozide	
Dronedarone	Probucol	
Droperidol	Procainamide	
Erythromycin	Propofol	
Escitalopram	Quinidine	
Flecainide	Roxithromycin	
Fluconazole	Sevoflurane	

Appendix 3
Drugs Known to Increase QT Interval

Information available at www.azcert.org.

Alfuzosin	Gemifloxacin	Prothipendyl
Apomorphine	Granisetron	Rilpivirine
Aripiprazole	Hydrocodone - ER	Risperidone
Artenimol+piperaquine	Iloperidone	Romidepsin
Asenapine	Imipramine (melipramine)	Saquinavir
Atomoxetine	Isradipine	Sertindole
Bedaquiline	Ketanserin	Sorafenib
Bendamustine	Lapatinib	Sunitinib
Bortezomib	Lenvatinib	Tacrolimus
Bosutinib	Leuprolide	Tamoxifen
Buprenorphine	Lithium	Telavancin
Capecitabine	Melperone	Telithromycin
Ceritinib	Mifepristone	Tetrabenazine
Clomipramine	Mirabegron	Tiapride
Clozapine	Mirtazapine	Tizanidine
Crizotinib	Moexipril/HCTZ	Tolterodine
Cyamemazine (cyamepromazine)	Nicardipine	Toremifene
Dabrafenib	Nilotinib	Trimipramine
Dasatinib	Norfloxacin	Tropisetron
Degarelix	Nortriptyline	Vardenafil
Delamanid	Ofloxacin	Vemurafenib
Desipramine	Osimertinib	Venlafaxine
Dexmedetomidine	Oxytocin	Vorinostat
Dolasetron	Paliperidone	Zotepine
Efavirenz	Panobinostat	
Eribulin mesylate	Pasireotide	
Ezogabine (Retigabine)	Pazopanib	
Famotidine	Perflutren lipid microspheres	
Felbamate	Perphenazine	
Fingolimod	Pilsicainide	
Flupentixol	Pipamperone	
Foscarnet	Promethazine	

Appendix 4
Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restrictions
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% 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 5
American Joint Committee on Cancer TNM Classification of Malignant Tumors

Definition of Primary Tumor (T) – Clinical and Pathological

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor $\leq$20 mm in greatest dimension
T1mi	Tumor $\leq$1 mm in greatest dimension
T1a	Tumor $>$1 mm but $\leq$5 mm in greatest dimension (round any measurement 1.0–1.9 to 2 mm)
T1b	Tumor $>$5 mm but $\leq$10 mm in greatest dimension
T1c	Tumor $>$10 mm but $\leq$20 mm in greatest dimension
T2	Tumor $>$20 mm but $\leq$50 mm in greatest dimension
T3	Tumor $>$50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma

Note: Lobular carcinoma in situ (LCIS) is a benign entity and has been removed from TNM staging in AJCC Cancer Staging Manual 8th edition.

Definition of Regional Lymph Nodes – Clinical (cN)

cN Category	cN Criteria
cNX [a]	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral Level I, II axillary lymph node(s)
cN1mi [b]	Micrometastases (approximately 200 cells, larger than 0.2 mm, but not larger than 2.0 mm
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases; or in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of the metastasis by sentinel node biopsy or fine-needle aspiration/ core needle biopsy respectively.

[a] The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.

[b] cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Definition of Regional Lymph Nodes – Pathological (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by RT-PCR; no ITCs detected
pN1	Micrometastases; or Metastases in 1–3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or micrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (Level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes

Definition of Regional Lymph Nodes – Pathological (pN) (cont.)

pN Category	pN Criteria
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastases to the infraclavicular (Level III axillary lymph) nodes.
pN3b	pN1a and pN2a in the presence of cN2b (positive internal mammary lymph nodes by imaging) or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

ITC = isolated tumor cell clusters; RT-PCR = reverse transcriptase polymerase chain reaction.

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of the metastasis by sentinel node biopsy or fine-needle aspiration/ core needle biopsy respectively, with no further resection nodes.

Distant Metastases (M)

M Category	M Criteria
M0	No clinical or radiographic evidence of distant metastases [a]
cM0(i+)	No clinical or radiographic evidence of distant metastases in presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other non-regional nodal tissue in a patient without symptoms or signs of metastases
M1	Distant metastases detected by clinical and radiographic means (cM) and/or histologically proven metastases larger than 0.2 mm (pM)

[a] Note that imaging studies are not required to assign the cM0 category.

Anatomic Stage/Prognostic Groups

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Note: T1 includes T1mi

T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

M0 includes M0(i+)

The designation pM0 is not valid; any M0 is clinical.

If a patient presents with M1 prior to neoadjuvant systemic therapy , the stage is Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.

Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression and provided the patient has not received neoadjuvant therapy.

Staging following neoadjuvant therapy is denoted with a “ye” or “yp” prefix to the T and N. No stage group is assigned if there is a complete pathological response (pCR) to neoadjuvant therapy for example, ypT0ypN0cM0.

Reference

Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017;589–631.