Official Title: A Randomized, Multicenter, Open-Label, Two-Arm, Phase II, Neoadjuvant Study Evaluating the Efficacy, Safety, and Pharmacokinetics of GDC-9545 Plus Palbociclib Compared With Anastrozole Plus Palbociclib for Postmenopausal Women With Estrogen Receptor-Positive and HER2-Negative Untreated Early Breast Cancer

NCT Number: NCT04436744

Document Date: Protocol Version 1: 08-April-2020

PROTOCOL

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, TWO-ARM, PHASE II, NEOADJUVANT STUDY EVALUATING THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF GDC-9545 PLUS PALBOCICLIB COMPARED WITH ANASTROZOLE PLUS PALBOCICLIB FOR POSTMENOPAUSAL WOMEN WITH ESTROGEN RECEPTOR-POSITIVE AND HER2-NEGATIVE UNTREATED EARLY BREAST CANCER**
PROTOCOL NUMBER:	WO42133
VERSION NUMBER:	1
EUDRACT NUMBER:	2020-001007-16
IND NUMBER:	132673
NCT NUMBER:	To be determined
TEST PRODUCT:	GDC-9545 (RO7197597)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
08-Apr-2020 23:34:09	Company Signatory	[redacted]

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PROTOCOL ACCEPTANCE FORM

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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 your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, TWO-ARM, PHASE II, NEOADJUVANT STUDY EVALUATING THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF GDC-9545 PLUS PALBOCICLIB COMPARED WITH ANASTROZOLE PLUS PALBOCICLIB FOR POSTMENOPAUSAL WOMEN WITH ESTROGEN RECEPTOR-POSITIVE AND HER2-NEGATIVE UNTREATED EARLY BREAST CANCER**
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NCT NUMBER:	To be determined
TEST PRODUCT:	GDC-9545 (RO7197597)
PHASE:	II
INDICATION:	Hormone receptor-positive postmenopausal women with untreated early breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib in postmenopausal patients with untreated estrogen receptor (ER)-positive and HER2-negative early breast cancer (EBC). Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments that may be assigned to a patient during the study (i.e., GDC-9545, GDC-9545 plus palbociclib, anastrozole, and anastrozole plus palbociclib).

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of GDC-9545 compared with anastrozole on the basis of the following endpoint:

- Central assessment of changes in Ki67 scores from baseline to Week 2 (Day 15 [+ 1 day])

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the clinical efficacy of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib on the basis of the following endpoints:

- Objective response rate by ultrasound, defined as the proportion of patients with a complete response or partial response, as determined by the investigator according to modified RECIST (mRECIST)
- Complete cell cycle arrest (CCCA) rate defined as proportion of patients with centrally assessed Ki67 scores ≤ 2.7% stained nuclei upon treatment at Week 2

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib on the basis of the following endpoints:

- Central assessment of changes in Ki67 scores from baseline to surgery and from Week 2 to surgery
- CCCA rate as defined as proportion of patients with centrally assessed Ki67 scores $\leq$ 2.7% stained nuclei upon treatment at surgery or post-treatment biopsy
- Pathological complete response rate (ypT0/is, ypN0) of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib

Safety Objectives

The safety objective for this study is to evaluate the safety of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined in accordance to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

The exploratory safety objective for this study is to evaluate the tolerability of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib from the patient's perspective on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities, as assessed through use of the NCI Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument
- Overall tolerability (i.e., bother experience due to side effects of treatment) as assessed through an overall treatment burden item
- Change from baseline in symptomatic treatment toxicities and overall tolerability and/or side effect burden, as assessed through respective use of the PRO-CTCAE and the additional overall burden item
- Expectations of therapy, feelings about side effects, and satisfaction with treatment from the patient perspective as assessed through use of the Cancer Therapy Satisfaction Questionnaire

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of GDC-9545 alone and when administered in combination with palbociclib on the basis of the following endpoint:

- Plasma concentration of GDC-9545 at specified timepoints

Biomarker Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to the study treatments (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with acquired resistance to the study treatments, can provide evidence of activity of the study treatments (i.e., pharmacodynamic 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, plasma, and tumor tissue and efficacy, safety, PK, disease biology, 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 (PgR) protein levels and ER target genes through analysis of matched baseline, Week 2, and surgery tumor specimens

Study Design

Description of Study

This is a randomized, multicenter, open-label, two-arm, Phase II study to evaluate the efficacy, safety, and pharmacokinetics of GDC-9545 versus anastrozole (in the window-of-opportunity phase) and GDC-9545 plus palbociclib compared with anastrozole plus palbociclib (in the neoadjuvant phase) in postmenopausal women with untreated ER-positive HER2-negative EBC. Approximately 215 patients are expected be enrolled in this study, at approximately 90 investigative sites globally.

Eligible patients will be randomly assigned in a 1:1 ratio to either the experimental arm (GDC-9545) or control arm (anastrozole). Patients must have histologically confirmed invasive breast carcinoma, with measurable disease as per mRECIST with a primary tumor size $\geq$ 1.5 cm in longest diameter evaluated by ultrasound at screening. The tumor size category at presentation should be cT1c ($\geq$ 1.5 cm)–cT4a–c.

Patients will be randomized on the basis of Ki67 score with eligibility criteria determined from pretreatment tumor tissue sample tested by a central pathology laboratory or a local site. Use of the central laboratory for Ki67 level testing is recommended and is the preferred method for determining eligibility and stratification. A Ki67 score $\geq$ 5% stained nuclei is required for eligibility. For the purpose of assessing eligibility, ER, PgR, and HER2 will be locally determined prior to beginning of study treatment. ER and PgR will also be centrally assessed, but the results are not required prior to randomization.

Patients will be stratified by T status (cT1c–cT2 vs. cT3–cT4 a–c), Ki67 score ($<$ 20% vs. $\geq$ 20%), and PgR status (positive vs. negative).

The study consists of a screening period of up to 28 days, a window-of-opportunity phase for 14 days, followed by a neoadjuvant treatment phase for 16 weeks (four 28-day cycles), surgery, and an end of study visit (28 days after the final dose of study treatment). During the window-of-opportunity phase, patients will receive either GDC-9545 or anastrozole as a single agent. During the neoadjuvant treatment phase, patients will receive four 28-day cycles of GDC-9545 plus palbociclib or anastrozole plus palbociclib.

All patients will be required to provide a pretreatment tumor tissue sample during screening, a tumor biopsy sample during treatment, and a post-treatment tissue sample from the surgical specimen.

In the neoadjuvant treatment phase, before each cycle, a blood sample will be collected and physical examination performed. Tumor assessments by ultrasound are mandatory at screening, and an additional tumor assessment by ultrasound must be performed after the final dose of neoadjuvant combination treatment (i.e., after Day 21 of Cycle 4 and prior to surgery). If there is suspicion of disease progression, any other method to evaluate the disease will be allowed at any time at investigator's discretion.

Surgery must be performed within a maximum of 14 days after the final cycle in the neoadjuvant treatment phase and ideally should occur as soon as possible after the last dose of study treatment. A surgical specimen will be obtained for analysis and will be analyzed by the local pathologist. If surgery is delayed, the patient is not operable or will not undergo surgery for other reasons, or does not complete 16 weeks (four cycles) of combination therapy, an optional biopsy may be performed as a separate procedure within 2 days from the end of the combination treatment.

All patients must return for the end of study visit 28 days after the final dose of study treatment regardless of the reason for treatment discontinuation. Patients who experience disease progression or unacceptable toxicity will be treated as per local practice after the end of study visit.

Patient treatment after the surgery will be at the investigator's discretion. Systemic chemotherapy and radiation therapy, if indicated, may be initiated after the end of study visit. Any post-surgery treatments are not part of the study and will not be provided by the Sponsor, and data will not be collected.

Patient-reported outcome instruments will be completed by patients to evaluate the experience of treatment from the patient's perspective as specified in the schedule of activities.

Patients who do not initially meet all eligibility criteria, other than HR status and Ki67, may be re-screened once to meet eligibility.

Number of Patients

Approximately 215 patients are expected be enrolled in this study, at approximately 90 investigative sites globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Postmenopausal 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 operable or inoperable invasive breast carcinoma, with all of the following characteristics:
  - cT1c (≥ 1.5 cm)– cT4a–c breast cancer at presentation

    Primary tumor must be ≥ 1.5 cm in longest diameter by ultrasound.
  - Measurable disease by ultrasound as defined per mRECIST
  - Patients with multifocal tumors (more than one mass confined to the same quadrant as the primary tumor) if all lesions are sampled and confirmed as ER-positive/HER2-negative invasive breast cancer and at least one lesion is ≥ 1.5 cm in longest diameter by ultrasound
  - Patients with multicentric tumors (multiple tumors involving more than one quadrant) if all discrete lesions are sampled and confirmed as ER-positive/HER2-negative invasive breast cancer and at least one lesion is ≥ 1.5 cm in longest diameter by ultrasound
- Candidate for neoadjuvant treatment and considered appropriate for endocrine therapy
- Willingness to undergo breast surgery (mastectomy or breast-conserving surgery) after neoadjuvant treatment
- Willingness to provide three mandatory tumor samples as follows:
  - Pretreatment
  - During treatment at Cycle 0 Day 15 (+1 day)
  - Posttreatment (from surgical specimen) or an optional biopsy (if surgery is not possible or delayed)
- Documented ER-positive tumor in accordance to American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines, assessed locally and defined as ≥ 1% of tumor cells stained positive on the basis of the most recent tumor biopsy
- Documented PgR status (positive or negative) as per local assessment
- Documented HER2-negative tumor in accordance to 2018 ASCO/CAP guidelines, assessed locally on the most recent tumor biopsy
- Ki67 score ≥ 5% analyzed centrally (recommended) or locally (by Sponsor pre-approved assay/scoring method)

  Use of the central laboratory for Ki67 level testing for eligibility is recommended.

For sites using the central laboratory to test for Ki67 eligibility, a tissue sample must be submitted to the central laboratory for enrollment by the immunohistochemistry-based central pathology laboratory Ki67 Clinical Trial Assay.

- Postmenopausal status defined as one of the following:
  - Documented bilateral surgical oophorectomy (≥ 14 days prior to first treatment on Day 1 of Cycle 1 and recovery from surgery to baseline)
  - Age ≥ 60 years and 12 consecutive months with no menses without an alternative medical cause
  - Age < 60 years and ≥ 12 continuous months of amenorrhea with no identified cause other than menopause, estradiol levels, and follicle-stimulating hormone levels in the postmenopausal range
- Eastern Cooperative Oncology Group Performance Status 0–1
- Adequate organ function as defined by the following criteria:
  - ANC ≥ 1.5×10^9/L (1500/μL)
  - Platelet count ≥ 100×10^9/L (100,000/μL)
  - AST and serum ALT ≤ 2 × upper limit of normal (ULN)
  - Hemoglobin ≥ 90 g/L (9 g/dL)
  - Serum bilirubin ≤ 1.5 × ULN with the following exception:

    Patients with known Gilbert syndrome: ≤ 3 × ULN
  - Serum creatinine ≤ 1.5 × ULN or estimated creatinine clearance ≥ 60 mL/min as calculated per institutional guidelines
- INR < 1.5 × ULN and aPTT < 1.5 × ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2 and 3 is required.

  For patients receiving heparin, PTT (or aPTT) between 1.5 and 2.5 × ULN (or patient value before starting heparin treatment) is required.

  If anticoagulation therapy is required for a prosthetic heart valve, stable INR between 2.5 and 3.5 is permitted.

Exclusion Criteria

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

- Stage IV (metastatic) breast cancer
- Inflammatory breast cancer (cT4d)
- Bilateral invasive breast cancer
- History of invasive breast cancer
- History of ductal carcinoma in situ or lobular carcinoma in situ if they have received any systemic therapy for treatment or radiation therapy to the ipsilateral breast

  Patients treated with surgery alone may be eligible.
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
- Previous systemic or local treatment for the primary breast cancer currently under investigation (including excisional biopsy or any other surgery of the primary tumor and/or axillary lymph nodes, radiotherapy, cytotoxic, and endocrine treatments)
- History of any prior treatment with aromatase inhibitors, tamoxifen, selective estrogen receptor downregulatorrs, or cyclin-dependent kinase 4 and 6 inhibitors

- Major surgery within 4 weeks prior to randomization
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including hepatitis (e.g., hepatitis B virus [HBV] or hepatitis C virus [HCV]), current alcohol abuse, cirrhosis, or positive test for viral hepatitis as defined below:

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

  Patients who test positive for HBcAb are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction is negative for HBV DNA.

  Patients who are positive for HCV serology are only eligible if testing for HCV RNA is negative.
- 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 anastrozole, or palbociclib or any of its excipients
- Known issues with swallowing oral medication
- History of documented hemorrhagic diathesis, coagulopathy, or thromboembolism
- Active cardiac disease or history of cardiac dysfunction including any of the following:
  - History or presence of symptomatic bradycardia or resting heart rate < 50 bpm at screening

    Patients on stable dose of a β-blocker or calcium channel antagonist for pre-existing baseline conditions (e.g., hypertension) may be permitted if resting heart is ≥ 50 bpm.
  - History of angina pectoris, symptomatic pericarditis, myocardial infarction, or any cardiac arrhythmias (e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality) within 12 months prior to study entry
  - History of documented congestive heart failure (New York Heart Association Class II–IV) or cardiomyopathy
  - Left ventricular ejection fraction $< 50\%$ as determined by multiple-gated acquisition scan or echocardiogram
  - QT interval corrected through use of Fridericia's formula (QTcF) > 470 ms based on mean value of triplicate ECGs, history of long or short QT syndrome, Brugada syndrome or known history of corrected QT interval prolongation, or torsades de pointes
  - 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, sick sinus syndrome, or evidence of prior myocardial infarction
  - 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 long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval
- Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or major upper gastrointestinal surgery including gastric resection
- Treatment with strong CYP3A4 inhibitors or inducers within 14 days or 5 drug elimination half-lives (whichever is longer) prior to randomization

- Known HIV infection
- Serious infection requiring oral or IV antibiotics, or other clinically significant infection within 14 days prior to screening

  Patients who fully recovered from serious and clinically significant infections within 14 days prior to screening are eligible.
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

End of Study

The end of this study is defined as the date when the last patient, last visit, occurs or the date of Sponsor decision to end the study, whichever is earlier. The end of the study is expected to occur approximately 6 months after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 19 months.

Investigational Medicinal Products

The investigational medicinal products for this study are GDC-9545 (test product), anastrozole (comparator), and palbociclib.

Test Product (Investigational Drug)

During the window-of-opportunity phase (14 days), patients will receive either GDC-9545 30 mg orally (PO) once a day (QD) or anastrozole 1 mg PO QD as a single agent. During the window-of-opportunity phase, GDC-9545 and anastrozole can be taken with or without food at approximately the same time each day.

During the neoadjuvant treatment phase, GDC-9545 30 mg PO QD or anastrozole 1 mg PO QD will be administered on Days 1–28 of each 28-day cycle in combination with palbociclib 125 mg PO QD on Days 1–21 of each 28-day cycle for four cycles. Starting with Day 1 of Cycle 0 and on Day 1 of each 28-day cycle thereafter, study treatment will be administered in the clinic after the study assessments, as indicated in the schedule of activities. All other doses will be taken at home on all non-clinic visit days. If a GDC-9545 dose is missed, the dose should be made up unless the next dose is due within 6 hours.

GDC-9545, anastrozole, and palbociclib should be taken orally with food at approximately the same time each day as per study treatment regimen. If palbociclib switches to tablet formation, study treatments may be taken with or without food.

Statistical Methods

Primary Analysis

The primary efficacy endpoint for this study is Ki67score change during the window-of-opportunity phase, defined as the mean change of Ki67 score from baseline to Week 2. Ki67 score will be centrally assessed and measured in percentage score. All Ki67 scores will be log-transformed before analysis, and 0.1 will be added to all raw Ki67 scores before log-transformation to handle zero raw Ki67 scores.

Mean Ki67 change at Week 2 will be summarized in original percentage scale for each arm, and corresponding 95% CI will be calculated by normal approximation. The change in mean Ki67 score between the experimental arm and control arm will be compared through the use of the z-test. Patients with missing central Ki67 scores at baseline and/or Week 2 will be excluded from the analysis.

The analysis of the primary efficacy endpoint will take place when approximately 202 patients have been randomized and have complete central Ki67 scores for the analysis at both baseline and Week 2.

Determination of Sample Size

The sample size is determined by the primary efficacy endpoint, central assessment Ki67 change from baseline to Week 2. Approximately 202 patients will need to be randomized in a 1:1 ratio to either the experimental arm (GDC-9545) or control arm (anastrozole) to allow for 80% power to detect an 8% improvement for mean Ki67 change in 2 weeks from −75% in the control arm to −83% in the experimental arm at one-sided 10% level of significance. This target improvement also corresponds to an effect size of 0.3. Based on Cohen's interpretation, an effect size of 0.3 represents a small to medium effect and a 21% non-overlap between the two treatment arms.

Patients with missing central Ki67 score at baseline and/or at Week 2 will be excluded from the analysis of the primary efficacy endpoint. For both experimental and control arms, a 6% missing Ki67 rate is assumed. Thus, a total of approximately 215 patients is projected to be enrolled to account for patients with missing Ki67 scores.

Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct an interim efficacy analysis. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by the Sponsor study team personnel who will have full access to unblinded data. Access to treatment assignment information will follow the Sponsor's standard procedures.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AI	aromatase inhibitor
ASCO	American Society of Clinical Oncology
ATAC	arimidex, tamoxifen, alone or in combination
CAP	College of American Pathologists
CBR	clinical benefit rate
CCCA	complete cell cycle arrest
CDK4/6	cyclin-dependent kinase 4 and 6
COVID-19	coronavirus disease 2019
CR	complete response
CTc	computed tomography
CTSQ	Cancer Therapy Satisfaction Questionnaire
DDI	drug-drug interaction
EBC	early breast cancer
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
FES	F-18 16α-fluoroestradiol
FFPE	formalin-fixed, paraffin-embedded core
FSH	follicle-stimulating hormone
GI	Gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hormone receptor
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system

Abbreviation	Definition
LHRH	luteinizing hormone–releasing hormone
mRECIST	modified Response Evaluation Criteria in Solid Tumors
NCI	National Cancer Institute
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NET	neoadjuvant endocrine therapy
NGS	next generation sequencing
OCT	optimal cutting temperature
ORR	objective response rate
pCR	pathological complete response
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic
PO	Oral
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Common Terminology Criteria for Adverse Events
QD	once a day
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SC	Steering Committee
SERD	selective estrogen receptor downregulatorr
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HORMONE-RECEPTOR POSITIVE BREAST CANCER

Breast cancer is the most commonly diagnosed cancer in women, with an estimated global incidence of 2,088,849 new cases and 626,679 deaths reported in 2018 (Bray et al. 2018; IARC 2018). Approximately 80% of all breast cancers express the estrogen receptor (ER), 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. The selective estrogen-receptor modulator, tamoxifen, and aromatase inhibitors (AIs) represent the cornerstone treatment for patients who are hormone receptor positive.

Selective ER downregulators (SERDs) have the potential to block endocrine-dependent and endocrine-independent ER signaling by ablation of ER and have been recognized to offer a therapeutic approach to ER-positive breast cancer in metastatic breast. Fulvestrant, the first generation SERD, binds, blocks, and degrades the ER, leading to complete inhibition of estrogen signaling through the ER. Fulvestrant has shown benefit over an AI (anastrozole) in frontline patients (Robertson et al. 2016; see Section 1.5.1). However, fulvestrant is hampered by intramuscular administration due to its poor physicochemical and pharmacokinetic (PK) properties.

GDC-9545, a second-generation SERD, is a novel, potent, orally bioavailable, small molecule therapeutic agent currently being developed for the treatment of patients with ER-positive breast cancer.

Tamoxifen and AI therapy are associated with significant side effects that often lead to early discontinuation of treatment. Maximizing therapeutic benefit, while minimizing treatment related toxicities, is particularly important in hormone receptor (HR)-positive, HER2-negative early breast cancer (EBC) where treatment duration is usually for 5 years or more. Currently, only approximately 60% of patients manage to complete 5 years of adjuvant endocrine therapy (Hagen et al. 2019). Improved treatment options may decrease or eliminate the risk of recurrences after adjuvant therapy and provide more tolerable treatment options (see Section 1.5.3).

1.2 BACKGROUND ON ANASTROZOLE IN EARLY BREAST CANCER

The AIs anastrozole, letrozole and exemestane have been the standard-of-care endocrine therapy in postmenopausal women with HR-positive EBC for 15 years. AIs, given either for 5 years or for 2–3 years after 2–3 years of tamoxifen, produce greater reductions in recurrence than 5 years of tamoxifen alone (Dowsett et al 2010), as well as reduction in breast cancer mortality (EBCTCG 2015).

In the Arimidex® (anastrozole), tamoxifen, alone or in combination (ATAC) trial (Howell et al. 2005), anastrozole has been shown to be superior to tamoxifen when given for 5 years as adjuvant treatment. After a median follow-up of 68 months, anastrozole significantly prolonged disease-free survival (hazard ratio=0.87; 95% CI: 0.78 to 0·97; p=0.01) and significantly reduced distant metastases (hazard ratio=0.86; 95% CI: 0.74 to 0·99; p=0.04) and contralateral breast cancers (42% reduction; 95% CI: 12 to 62; p=0.01). Anastrozole was also associated with fewer side-effects than tamoxifen, especially gynecological problems and vascular events, but arthralgia and fractures were increased.

Anastrozole has also been assessed in several neoadjuvant studies. The IMPACT trial evaluated change in expression of the proliferative marker Ki67 with anastrozole, tamoxifen, or combination in the neoadjuvant setting. The suppression of Ki67 was greater with anastrozole than with tamoxifen (p=0.004 and $p < 0.001$) but was similar between tamoxifen and the combination (p=0.600 and p=0.912, respectively; Smith et al. 2005) (see Section 1.5.3).

1.3 BACKGROUND ON CDK4/6 INHIBITORS IN BREAST CANCER

Three cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, palbociclib, ribociclib, and abemaciclib, are now in widespread clinical use and have been approved as both first–line and second–line treatments in patients with HR-positive, HER2-negative breast cancer. With the exception of abemaciclib, these agents are approved for use only in combination with endocrine agents, typically with an AI in the first-line setting or with fulvestrant in patients who are AI-resistant. When given in combination with endocrine therapy, an approximate doubling of progression-free survival (PFS) in patients with advanced HR-positive, HER2-negative breast cancer, compared with endocrine therapy plus placebo, has been observed. These consistently positive PFS results have been demonstrated in large Phase III trials in the frontline setting (PALOMA-2 [Finn et al. 2015] for palbociclib plus letrozole; MONALEESA-2 [Slamon et al. 2018] for ribociclib plus letrozole; and MONARCH-3 [Goetz et al. 2017] for abemaciclib plus letrozole or anastrozole). More recently, the MONALEESA-7 trial was the first to show a statistically significant improvement in overall survival for a CDK4/6 inhibitor (ribociclib plus endocrine therapy) in breast cancer and the first to evaluate this treatment exclusively in premenopausal patients (Im et al. 2019). Additionally, benefit was observed in populations previously treated with endocrine therapy for advanced disease (PALOMA-3 [Cristofanilli et al. 2016] for palbociclib plus fulvestrant; MONARCH-2 [Sledge et al. 2017] for abemaciclib and fulvestrant; and MONALEESA-3 [Goetz et al. 2017] for ribociclib plus fulvestrant).

In the neoadjuvant setting, the addition of CDK4/6 inhibitors to AIs has been shown to significantly decrease Ki67 expression and lead to potent cell cycle arrest effect. Refer to Section 1.5.3 for the rationale for using CDK4/6 inhibitors in the neoadjuvant setting.

CDK 4/6 inhibitors are currently being explored in the adjuvant and postneoadjuvant EBC setting.

1.4 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 of both wild-type and mutant ER with nanomolar potency. Upon binding, GDC-9545 induces an inactive conformation to the ER ligand-binding domain, 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 ER-α 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 modulators such as tamoxifen that 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 ERs.

1.4.1 Nonclinical Data

Nonclinical studies comparing drug exposure and in vitro potency of GDC-9545 versus fulvestrant demonstrated that human steady-state total drug exposure of GDC-9545 at 30 mg once a day (QD) is approximately 10-fold higher than the steady-state exposure of fulvestrant 500 mg intramuscular monthly. Furthermore, the lower plasma protein binding of GDC-9545 provides higher free concentration of GDC-9545 than fulvestrant. In in vitro cell and biochemical assays, GDC-9545 exhibited up to 10-times higher potency than fulvestrant both in wild-type and *ESR1*–mutant contexts.

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 activating *ESR1* mutation (ER. Y537S). The efficacious dose range was 0.1–10 mg/kg/day, and all doses were well tolerated. On the basis of in vivo xenograft models, maximal activity of GDC-9545 occurs at human dose equivalents greater than 10 mg. In three patient-derived xenograft models, no further ER depletion or inhibition of ER transcriptional activity was observed with the increase of dose from 20–80 mg/kg, corresponding to clinical exposures of 30 mg and 100 mg, respectively. Fulvestrant, when dosed according to a clinically relevant dosing scheme, was less efficacious than GDC-9545 in the assessed xenograft models. Taken together, GDC-9545 data demonstrated robust nonclinical activity in ER-positive breast cancer models of both *ESR1*–wild type and *ESR1*-mutation–bearing disease**.**

Refer to the GDC-9545 Investigator's Brochure for details on toxicology and safety pharmacology studies.

1.4.2 Clinical Data

GDC-9545 Experience in Early Breast Cancer

Study GO40987 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. Patients are assigned to one of three treatment cohorts (10, 30, and 100 mg). GDC-9545 is administered QD up to and including the day of surgery (if allowed per local process) for approximately 14 days. All patients are required to provide a pretreatment and post-treatment tumor tissue sample.

As of 31 January 2020 preliminary data, approximately 28 patients have been enrolled and 24 patients have completed study treatment and surgery with no surgical complications attributed to GDC-9545. To date, no patients treated have experienced any thromboembolic events or issues with wound healing. No serious adverse events or Grade ≥3 adverse events related to GDC-9545 have been reported. No patients withdrew from study due to adverse events. Overall, all of the reported adverse events have been Grade 1 or 2 in severity and in keeping with the expected safety profile of drugs in this class and the GDC-9545 Phase I metastatic breast cancer study.

GDC-9545 Experience in Metastatic Breast Cancer

GDC-9545 is currently being evaluated in Study GO39932, a first-in-human, Phase Ia/Ib, multicenter, open-label study evaluating the safety, pharmacokinetics, and activity of GDC-9545 as a single agent or in combination with palbociclib (± luteinizing hormone–releasing hormone [LHRH] agonist) in patients with ER-positive (HER2-negative) locally advanced or metastatic breast cancer.

As of the clinical cutoff date of 4 September 2019, 120 patients in Study GO39932 had received treatment as follows: 74 patients had been treated with single-agent GDC-9545 at doses of 10 mg (6 patients), 30 mg (10 patients), 90/100 mg (correlated to 90 or 100 mg)(49 patients), and 250 mg (9 patients) (with or without LHRH agonist), and 46 patients had been treated with GDC-9545 100 mg in combination with palbociclib 125 mg (with or without LHRH agonist). Overall, study patients had received a median of 113 doses of GDC-9545 (range: 3–596 doses) and remained on GDC-9545 treatment for a median of 113 days (range: 3–531 days). Enrollment is currently ongoing in the expansion stage, where an additional 30 patients will be dosed with GDC-9545 monotherapy at 30 mg QD (see Section 3.3.1).

The majority of patients enrolled as of the clinical cutoff date had visceral (62%) and measurable disease (79%) at baseline, and a small proportion (18%) had bone-only disease at baseline. Baseline *ESR1* mutation status of wild-type or mutant was reported in 55% and 33% of patients, respectively. The remaining patients had unknown *ESR1* mutation status. The majority of patients did not receive prior therapy with fulvestrant (83%) or a CDK4/6 inhibitor (71%).

Based on the clinical cutoff date, clinical benefit, as measured by either radiographic partial response (PR) or at least 6 months of stable disease, was observed at all four single-agent GDC-9545 doses tested and in the GDC-9545 plus palbociclib combination cohort. In the single-agent GDC-9545 30 mg cohort, there were 10 efficacy-evaluable patients (defined as any patient with at least one dose of study treatment) and 7 response-evaluable patients with measurable disease per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) at baseline. In this cohort, the median for investigator-assessed PFS per RECIST v1.1 for the 10 efficacy-evaluable patients was 231 days (95% CI: 54, not evaluable), with 50% of patients reporting an event of disease progression or death. The clinical benefit rate (CBR) in all patients in the 30 mg cohort was 50.0% and the objective response rate (ORR; confirmed response) in the 7 response-evaluable patients was 14.3% (1 patient). The CBR was similar to that observed in patients treated at higher doses (e.g., at 90/10 0mg, CBR was 53.6% [95% CI: 38% to 69%; n = 36]).

Adverse Events, Regardless of Attribution

Of the 74 patients treated with single-agent GDC-9545 at doses ranging from 10 to 250 mg, adverse events, regardless of attribution and occurring in 10% or more patients, included the following: fatigue (24%), back pain (20%), arthralgia (19%), diarrhea (16%), nausea (16%), constipation (15%), pain in extremity (15%), cough (12%), and dizziness (11%). Adverse events mapped into the cardiac disorder System Organ Class were experienced by 7 patients (9.5%), including adverse events of bradycardia (6 patients at 90/100 mg and 1 patient at 250 mg) and palpitation (1 patient at 90 mg and 1 patient at 250 mg). All cardiac-related events were Grade 1 and asymptomatic. No cardiac-related events have been reported at the GDC-9545 30-mg dose.

Of the 10 patients treated with single-agent GDC-9545 30 mg, the following adverse events occurred in 3 or more patients: fatigue, nausea, constipation, back pain and vomiting (4 patients each), diarrhea, pain in extremity, gastroesophageal reflux disease, dyspepsia and myalgia (3 patients each).

Of the 46 patients treated with GDC-9545 100 mg in combination with palbociclib 125 mg, adverse events, regardless of attribution and occurring in 10% or more patients, included the following: neutropenia/neutrophil count decrease (67%); bradycardia (26%); fatigue (24%); diarrhea (22%); nausea, constipation, dizziness, and anemia (17% each); asthenia 15%); thrombocytopenia (13%); and pruritus and visual impairment (11% each).

Overall in Study GO39932, Grade ≥ 3 adverse events were reported in 40 of 120 safety-evaluable patients (33%), including 14 patients (19%) in single-agent GDC-9545 cohorts, and 26 patients (57%) in the GDC-9545 plus palbociclib combination cohorts. Grade ≥3 adverse events, regardless of attribution and occurring in 2 or more patients, were lymphopenia and diarrhea (3%) in single-agent GDC-9545 cohorts and neutropenia/neutrophil count decrease (50%) in GDC-9545 plus palbociclib combination cohorts. No Grade ≥ 3 adverse events were reported in the GDC-9545 30-mg cohort.

Serious adverse events were reported in 8 of 120 (6.7%) safety-evaluable patients, including 4 of 74 (5.4%) patients in the single-agent GDC-9545 cohort and 4 of 46 (8.7%) patients in the GDC-9545 plus palbociclib combination cohort. One case of Grade 3 migraine occurred in the 30 mg single-dose cohort. Three Grade 3 serious adverse event cases occurred in the 90/100 mg single-dose cohort: appendiceal abscess, small intestinal obstruction, and fatigue. In the GDC-9545 plus palbociclib cohort, one Grade 3 urinary tract infection occurred, and three Grade 4 cases occurred: neutropenia (2 cases) and thrombocytopenia.

Overall, no Grade 5 adverse events were reported.

Adverse Events Attributed to Study Treatment

Of the 74 patients treated with single-agent GDC-9545 at doses ranging from 10–250 mg, adverse events attributed to GDC-9545 have been mostly Grade 1 or 2 in severity. Adverse events attributed to GDC-9545 occurring in 5% or more patients included the following: fatigue (19%); arthralgia (12%); nausea (11%); diarrhea (10%); bradycardia (8%); hot flush, alanine aminotransferase increase, and aspartate aminotransferase increase (7% each); and constipation and dyspepsia (5% each).
Of the 10 patients treated with single-agent GDC-9545 at 30 mg, adverse events attributed to GDC-9545 with Grade 1 or 2 severity occurring in 3 or more patients included fatigue, nausea, diarrhea, and dyspepsia (3 patients each). Three Grade 3 events of fatigue, transaminase increase, and diarrhea were reported in patients treated with GDC-9545 100 mg. Only one patient experienced a treatment-related serious adverse event (Grade 3 fatigue) considered related to both GDC-9545 and disease progression. No patients were withdrawn from treatment because of adverse events.

Of the 46 patients treated with GDC-9545 100 mg in combination with palbociclib 125 mg, adverse events attributed to any study drug occurring in 5% or more patients included the following: neutropenia/neutrophil count decrease (63%); bradycardia (24%); fatigue (20%); nausea (17%); diarrhea (15%); anemia, asthenia, and thrombocytopenia (13% each); pruritus (11%); hot flush, constipation, dizziness, and visual impairment (9% each); and dry skin, vomiting, vision blurred, decreased appetite, insomnia, lymphocyte count decrease, photopsia, and alopecia (7% each).

A total of 4 patients exposed to the combination experienced serious adverse events (urinary tract infection, thrombocytopenia, and 2 serious cases of neutropenia), none of which were assessed as related to GDC-9545. The only Grade $\geq$3 adverse event affecting $\geq$2 patients was neutropenia, including 2 patients with Grade 4 neutropenia. There were no adverse events with fatal outcome, and no patients treated with the combination experienced adverse events leading to discontinuation from treatment.

Overall, GDC-9545 was well tolerated at all dose levels with no trend for an increase in frequency or severity of adverse events. Seven (9.5%) patients who received single-agent GDC-9545 (all treated at 90 mg or higher dose) reported Grade 1

asymptomatic bradycardia/sinus bradycardia. No adverse event of bradycardia was reported at the 30-mg dose. The mean heart rate decrease was approximately 3 bpm at the dose of 30 mg on Cycle 1 Day 15 and stabilized during the treatment. Combination therapy of GDC-9545 100 mg with palbociclib 125 mg in 46 patients has not identified any new safety signals or overlapping toxicities. It is therefore anticipated that GDC-9545 30 mg administered with palbociclib 125 mg will be well tolerated (see Section 3.3.1).

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

1.5 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The current trial is a proof of concept Phase II study in postmenopausal patients with ER-positive HER2-negative newly diagnosed EBC. The study will have two parts, a 14-day window-of-opportunity phase followed by a 16-week neoadjuvant treatment phase.

1.5.1 Rationale for Exploring GDC-9545 in Early Breast Cancer

Despite the effectiveness of both tamoxifen and AI therapy, many patients ultimately relapse or develop resistance to these agents. The resistance to endocrine therapy is often caused by *ESR1* mutation (Angus et al. 2017). Whereas *ESR1* mutations are relatively rare in primary breast cancer, they are more prevalent in metastatic cancers, especially in patients previously treated with AIs, 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 AIs and tamoxifen ineffective (Robinson et al. 2013; Jeselsohn et al. 2014).

In contrast to AIs and tamoxifen, selective ER degraders (SERDs) are efficacious against these ligand-independent, constitutively active ER-mutated receptors. This was first shown in the SoFEA study (Johnston et al. 2013), a Phase III randomized study in postmenopausal patients with HR-positive locally advanced or metastatic breast cancer comparing fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal AIs. Subgroup analysis revealed that patients with *ESR1* mutations had an improved PFS of 5.7 months with fulvestrant compared with 2.6 months with exemestane (hazard ratio=0.52; 95% CI: 0.30 to 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 detection of *ESR1* mutations. The FALCON study was a Phase III, randomized, double-blind study that treated patients with de novo locally advanced or metastatic HR-positive breast cancer with either fulvestrant or anastrozole (Robertson et al. 2016). Fulvestrant was associated with a statistically significant improvement in PFS compared with anastrozole (hazard ratio=0.797; 95% CI: 0.637 to 0.999; p=0.0486).

Median PFS was 16.6 months (95% CI: 13.83 to 20.99 months) with fulvestrant and 13.8 months (95% CI: 11.99 to 16.59 months) with anastrozole (a difference in medians of 2.8 months).

Fulvestrant has poor PK properties, requiring bilateral intramuscular injection, which has prohibited it from being studied in large adjuvant trials. Therefore, studies are needed that aim to evaluate new oral SERDS with superior bioavailability, pharmacokinetics, and more potent activity against the ER, including *ESR1* mutations. These novel agents have the potential to be more effective than AIs in preventing disease progression and thus may ultimately improve overall survival in women with ER-positive EBC.

There is a need to improve the tolerability of endocrine therapies, particularly since treatment is usually for 5 years or more. Currently approved therapies are associated with significant side effects that often lead to early discontinuation of treatment. Tamoxifen may cause venous thromboembolism and uterine cancer (Mourits et al. 2001; Hernandez et al. 2009), and AIs cause accelerated bone loss and arthralgia (Muslimani et al. 2009). Currently, only approximately 60% of patients manage to complete 5 years of adjuvant endocrine therapy (Hagen et al. 2019). Oral SERDs may provide a more tolerable treatment option that enables better adherence and thus maximizes therapeutic benefit and compliance.

1.5.2 Rationale for the Window-of-Opportunity Phase

In the window-of-opportunity phase, patients will be treated with either GDC-9545 or anastrozole for 2 weeks, followed by a biopsy to assess Ki67 change from baseline. Studies using a window-of-opportunity are becoming the standard for developing new treatments in HR–positive EBC. These studies allow for access to tumor tissue before, during, and after treatment for pharmacodynamics and correlative evaluations; provide critical insight into the optimal patient population, differences in activity and mechanisms between agents; and influence of the tumor biology on sensitivity and molecular mechanisms of response or resistance (Guerrero-Zotano and Arteaga 2017).

The primary efficacy endpoint of the study will be the reduction of Ki67, a well-established proliferation biomarker, after 2 weeks of treatment (compared with baseline). 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). Refer to Section 3.3.4.1 for a summary of the available evidence regarding the predictive value of changes in Ki67 on long-term outcome in EBC.

1.5.3 Rationale for the Neoadjuvant Phase

In the neoadjuvant phase, patients will be treated with GDC-9545 plus the CDK4/6 inhibitor palbociclib or with anastrozole plus palbociclib for 16 weeks.

Neoadjuvant endocrine therapy (NET), given from 4 to 6 months, has been shown to effectively reduce tumor size and potentially reduce the extent of surgery (Guerrero-Zotano and Arteaga 2017). Aside from the potential clinical benefits achieved by downstaging, neoadjuvant therapy allows for direct and early observation of treatment response and provides prognostic information. This is of immediate benefit to patients. Patients who were not initially candidates for chemotherapy but whose tumors do not respond to NET can be offered chemotherapy after surgery as an additional treatment option. Patients who were initially candidates for chemotherapy and who have a good response to NET may be able to continue adjuvant treatment without the addition of chemotherapy.

CDK4/6 inhibitors are already established as standard-of-care treatment in patients with advanced HR-positive, HER2-negative breast cancer (see Section 1.3. for a summary of the clinical evidence with CDK4/6 inhibitors in advanced breast cancer). These inhibitors are currently being actively explored in the EBC setting, including neoadjuvant, adjuvant, and post-neoadjuvant studies (Spring et al. 2019).

The addition of CDK4/6 inhibitors to AIs has been shown to significantly increase the antiproliferative effect (see Section 3.3.4.1 for a summary of the available evidence for Ki67 changes as a predictor of long-term outcome in adjuvant studies). In the neoadjuvant Phase II NeoPalAna study (Ma et al. 2017), the combination of palbociclib plus anastrozole achieved 87% complete cell cycle arrest (CCCA) compared with 26% with anastrozole alone ($p < 0.001$). Similarly, in the PALLET trial, more patients on palbociclib plus letrozole achieved CCCA compared with letrozole alone (90% vs. 59%; p=0.001) (Johnston et al. 2019). The addition of abemaciclib to anastrozole was shown to significantly reduce Ki67 compared with anastrozole alone in the neoMONARCH study (Martin et al. 2018).

The safety findings in the PALLET and neoMONARCH trials suggest that the tolerability of CDK4/6 inhibitors in the EBC setting is comparable with the experience from advanced breast cancer. In the PALLET study, more patients had Grade ≥ 3 toxicity on palbociclib plus letrozole than on letrozole alone (49.8% vs. 17.0%; $p < 0.001$) mainly because of asymptomatic neutropenia (40.8% vs. 0%) (Johnston et al. 2019). Grade 3 ALT increase was reported for 4% of patients in the palbociclib plus letrozole arm, versus 0% with letrozole alone arm. The most common adverse event reported in more than 20% of the patients receiving the combination of palbociclib and letrozole were fatigue (58.2%), neutrophil count decreased (54.7%), hot flushes (26.9%), and nausea (24.9%).

The secondary efficacy endpoint of this study is ORR of the primary breast tumor after 16 weeks (four cycles) of neoadjuvant treatment, measured by ultrasound. Achieving a reduction in tumor size is associated with a benefit for patients because it often allows for less extensive surgery than originally planned (Guerrero-Zotano and Arteaga 2017). The combination of palbociclib and AI showed clinical benefit with response rates of 41%

and 55.3% (both measured by ultrasound) in the NeoPalAna and PALLET trials after 14–16 weeks of neoadjuvant treatment (Ma et al. 2017; Johnston et al. 2019).

ORR is not a co-primary endpoint of the study because its validity in predicting long-term outcome in EBC has not yet been fully established, with prior studies showing inconsistent results (Semiglazov 2015). In the IMPACT study, there was no difference among the three arms with regard to objective response (anastrozole 37%, tamoxifen 36%, and the combination 39%). ORR did not predict long-term outcome in the adjuvant ATAC study, in which anastrozole achieved a significantly superior disease-free survival compared with tamoxifen or the combination (Smith et al. 2005). In contrast, the P024 study demonstrated a significantly higher clinical response with the AI letrozole compared with tamoxifen (55% vs. 36%; $p < 0.01$). The safety and activity of CDK4/6 inhibitors in combination with endocrine therapy observed in patients with ER-positive, HER2-negative breast cancer demonstrated in the NeoPalAna, PALLET, and neoMONARCH studies warrants the investigation of the combination of GDC-9545 with palbociclib in this group of patients.

The anticipated or potential adverse events associated with administration of GDC-9545 in combination with palbociclib therapy are expected to be clinically monitorable, manageable, and reversible in patients (see Section 5). The study will also evaluate patient-reported tolerability for symptoms that have been associated with treatment and are self-reportable.

This study will provide critical pharmacodynamic data and rich biomarker data to help select patients whose tumors will respond or have resistance, will augment our current understanding of the safety of this combination, and will provide early evidence of efficacy in the curative setting—a setting where new therapies with an improved therapeutic index are needed.

Improved treatment options for ER-positive, HER2-negative breast cancer may provide more effective and tolerable treatment, decrease or eliminate the risk of late recurrences after adjuvant therapy, and thus, ultimately achieve an increased cure rate for patients with ER-positive, HER2-negative EBC.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib in postmenopausal patients with untreated ER-positive and HER2-negative EBC. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, “study treatment” refers to the combination of treatments that may be assigned to a patient during the study (i.e., GDC-9545, GDC-9545 plus palbociclib, anastrozole, and anastrozole plus palbociclib).

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of GDC-9545 compared with anastrozole on the basis of the following endpoint:

- Central assessment of changes in Ki67 scores from baseline to Week 2 (Day 15 [+1 day])

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the clinical efficacy of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib on the basis of the following endpoints:

- ORR by ultrasound, defined as the proportion of patients with a complete response (CR) or PR, as determined by the investigator according to modified RECIST (mRECIST)
- CCCA rate defined as proportion of patients with centrally assessed Ki67 scores ≤2.7% stained nuclei upon treatment at Week 2

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib on the basis of the following endpoints:

- Central assessment of changes in Ki67 scores from baseline to surgery and from Week 2 to surgery
- CCCA rate as defined as proportion of patients with centrally assessed Ki67 scores ≤2.7% stained nuclei upon treatment at surgery or post-treatment biopsy (see Section 4.5.10)
- Pathological complete response (pCR) rate (ypT0/is, ypN0) of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined in accordance to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

The exploratory safety objective for this study is to evaluate the tolerability of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib from the patient's perspective on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities, as assessed through use of the NCI Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument
- Overall tolerability (i.e., bother experience due to side effects of treatment) as assessed through an overall treatment burden item
- Change from baseline in symptomatic treatment toxicities and overall tolerability and/or side effect burden, as assessed through respective use of the PRO-CTCAE and the additional overall burden item
- Expectations of therapy, feelings about side effects, and satisfaction with treatment from the patient perspective as assessed through use of the Cancer Therapy Satisfaction Questionnaire (CTSQ)

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the PK profile of GDC-9545 alone and when administered in combination with palbociclib on the basis of the following endpoint:

- Plasma concentration of GDC-9545 at specified timepoints

2.4 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to the study treatments (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with acquired resistance to the study treatments, can provide evidence of activity of the study treatments (i.e., pharmacodynamic 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, plasma, and tumor tissue (listed in Section 4.5.12) and efficacy, safety, PK, disease biology, 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 (PgR) protein levels and ER target genes through analysis of matched baseline, Week 2, and surgery tumor specimens

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a randomized, multicenter, open-label, two-arm, Phase II study to evaluate the efficacy, safety, and pharmacokinetics of GDC-9545 versus anastrozole (in the window-of-opportunity phase) and GDC-9545 plus palbociclib compared with

anastrozole plus palbociclib (in the neoadjuvant phase) in postmenopausal women with untreated ER-positive HER2-negative EBC. Approximately 215 patients are expected be enrolled in this study, at approximately 90 investigative sites globally.

Eligible patients will be randomly assigned in a 1:1 ratio to either the experimental arm (GDC-9545) or control arm (anastrozole). Patients must have histologically confirmed invasive breast carcinoma, with measurable disease as per mRECIST with a primary tumor size ≥1.5 cm in longest diameter evaluated by ultrasound at screening. The tumor size category at presentation should be cT1c (≥1.5 cm)–cT4a–c.

Patients will be randomized on the basis of Ki67 score with eligibility criteria determined from pretreatment tumor tissue sample tested by a central pathology laboratory or a local site. Use of the central laboratory for Ki67 level testing is recommended and is the preferred method for determining eligibility and stratification (see Section 4.5.10). A Ki67 score ≥5% stained nuclei is required for eligibility (see Section 4.1.1). For the purpose of assessing eligibility, ER, PgR, and HER2 will be locally determined prior to beginning of study treatment. ER and PgR will also be centrally assessed, but the results are not required prior to randomization.

Patients will be stratified by T status (cT1c–cT2 vs. cT3–cT4 a–c) (Hortobagyi et al. 2017), Ki67 score (<20% vs. ≥20%), and PgR status (positive vs. negative).

The study consists of a screening period of up to 28 days, a window-of-opportunity phase for 14 days, followed by a neoadjuvant treatment phase for 16 weeks (four 28-day cycles), surgery, and an end of study visit (28 days after the final dose of study treatment). During the window-of-opportunity phase, patients will receive either GDC-9545 or anastrozole as a single agent. During the neoadjuvant treatment phase, patients will receive four 28-day cycles of GDC-9545 plus palbociclib or anastrozole plus palbociclib.

All patients will be required to provide a pretreatment tumor tissue sample during screening, a tumor biopsy sample during treatment, and a post-treatment tissue sample from the surgical specimen (see Section 4.5.10).

In the neoadjuvant treatment phase, before each cycle, a blood sample will be collected and physical examination performed (see Appendix 1 and Appendix 2). Tumor assessments by ultrasound are mandatory at screening, and an additional tumor assessment by ultrasound must be performed after the final dose of neoadjuvant combination treatment (i.e., after Day 21 of Cycle 4 and prior to surgery). If there is suspicion of disease progression, any other method to evaluate the disease will be allowed at any time at investigator's discretion (see Appendix 1).

Surgery must be performed within a maximum of 14 days after the final cycle in the neoadjuvant treatment phase and ideally should occur as soon as possible after the last dose of study treatment. A surgical specimen will be obtained for analysis and will be analyzed by the local pathologist. If surgery is delayed, the patient is not operable or will not undergo surgery for other reasons, or does not complete 16 weeks (four cycles) of combination therapy, an optional biopsy may be performed as a separate procedure within 2 days from the end of the combination treatment.

All patients must return for the end of study visit 28 days after the final dose of study treatment regardless of the reason for treatment discontinuation. Patients who experience disease progression or unacceptable toxicity will be treated as per local practice after the end of study visit.

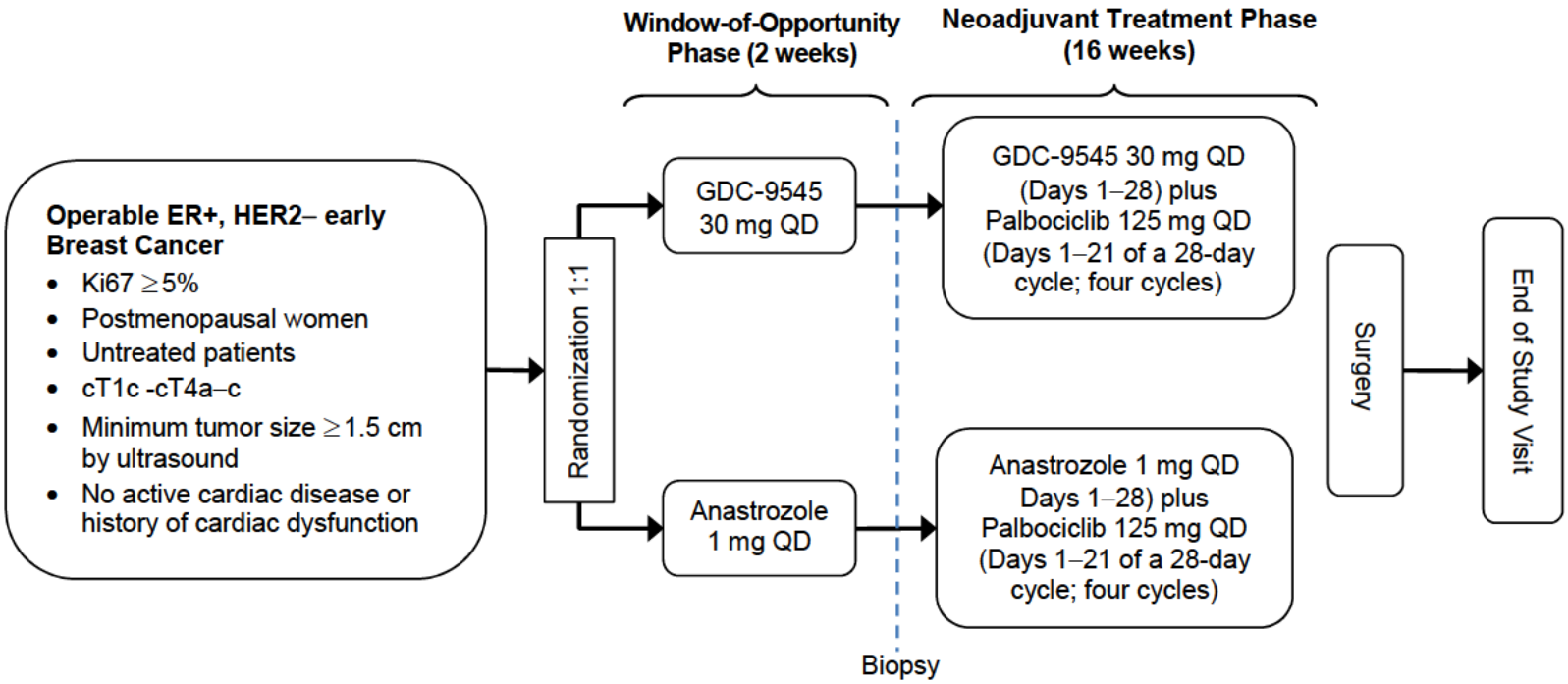
Patient treatment after the surgery will be at the investigator's discretion. Systemic chemotherapy and radiation therapy, if indicated, may be initiated after the end of study visit. Any post-surgery treatments are not part of the study and will not be provided by the Sponsor, and data will not be collected.

Patient-reported outcome (PRO) instruments will be completed by patients to evaluate the experience of treatment from the patient's perspective as specified in the schedule of activities (see Appendix 1).

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1 and Appendix 2.

Patients who do not initially meet all eligibility criteria, other than HR status and Ki67, may be re-screened once to meet eligibility. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

Figure 1 Study Schema



ER+= estrogen receptor-positive; HER2–=HER2–negative; QD=once a day.
Patients will be stratified by T status (cT1c–cT2 vs. cT3–cT4 a–c) (Hortobagyi et al. 2017), Ki67 score (<20% vs. ≥20%), and progesterone receptor status (positive vs. negative).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit, occurs or the date of Sponsor decision to end the study, whichever is earlier. The end of the study is expected to occur approximately 6 months after the last patient is enrolled.

The Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 19 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for GDC-9545 and Palbociclib Dose and Schedule

This study will evaluate GDC-9545 30 mg taken orally (PO) QD as a single agent for 2 weeks during the window-of-opportunity phase. This will be followed by the neoadjuvant phase that will evaluate GDC-9545 30 mg PO QD on Days 1–28 of each cycle plus palbociclib 125 mg PO QD on Days 1–21 of each 28−day cycle, beginning on Day 1 of Cycle 1. The dose of palbociclib administered represents the currently approved dosage for the treatment of adult patients with HR-positive/HER2-negative advanced or metastatic breast cancer.

Based on the totality of the nonclinical and clinical data, GDC-9545 30 mg taken PO QD in combination with palbociclib has been selected as the most appropriate Phase II dose and schedule to maximize efficacy while ensuring tolerability.

The Phase Ia/Ib Study GO39932 in metastatic breast cancer evaluated escalating doses of GDC-9545 from 10 mg PO QD to 250 mg PO QD. Overall, GDC-9545 was shown to be well tolerated at all dose levels with no clear trend for an increase in frequency or severity of adverse events, except for Grade 1 asymptomatic bradycardia/heart rate decrease that was dose related. Preclinical in vivo xenograft models reveal that the maximal activity is saturated at doses above 10-mg human-dose equivalents. Human steady-state total drug exposure of GDC-9545 at 30 mg QD is about 10-fold higher than the steady-state exposure of fulvestrant 500 mg intramuscular monthly, with higher in vitro potency. F-18 16α-fluoroestradiol (FES)–positron emission tomography (PET) showed complete or near-complete ($>$90%) suppression of FES uptake to background levels at 10 mg PO QD to 250 mg PO QD regardless of *ESR1* mutation status. Clinical activity as measured by CBR was approximately 50% at the dose of 30 mg QD. No evidence of additional benefit was observed at doses above 30 mg. Similar pharmacodynamic reductions in ER, PgR, and Ki67 protein levels and in ER-signaling activity as measured by gene expression were observed across all dose levels, regardless of *ESR1* mutation status.

The combination of GDC-9545 and palbociclib was also evaluated in the GO39932 study. As of the cutoff date of 4 September 2019, 46 patients were treated with GDC-9545

100 mg PO QD and palbociclib 125 mg PO QD. In general, the combination was well tolerated with an expected safety profile, and no safety signals were identified.

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

3.3.2 Rationale for Patient Population

Postmenopausal patients with untreated, ER-positive, HER2-negative early stage breast cancer will be enrolled in this study. 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, a breast tumor size of $\geq$1.5 cm as measured by ultrasound is needed for the study. Premenopausal patients are excluded because the control arm treatment includes anastrozole, which is not indicated in patients with functioning ovaries.

3.3.3 Rationale for Control Group

Anastrozole is an AI approved by the U.S. Food and Drug Administration (FDA) in the adjuvant setting for EBC. The approval was based on the results of the ATAC trial, where 9,366 postmenopausal women with operable breast cancer were randomized to adjuvant treatment with anastrozole 1 mg QD, tamoxifen 20 mg QD, or a combination of the two treatments for 5 years or until recurrence of the disease (Howell et al. 2005).

Anastrozole has not been approved in the neoadjuvant setting; however, neoadjuvant trials have consistently shown superiority of anastrozole or letrozole over tamoxifen in Ki67 suppression and clinical response and have predicted the outcome of subsequent adjuvant studies (Dowsett et al. 2005a, 2005b, 2007; Ellis et al. 2008; see biomarker Section 3.3.4.1 for additional details).

More recently, combinations of hormonal therapy with CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) have shown robust efficacy benefit in the ER-positive advanced breast cancer setting (see Section 1.3) and promising antiproliferative and clinical effects in EBC (see Section 1.5.3).

3.3.4 Rationale for Biomarker Assessments

ER-positive, HER2-negative 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. Pharmacodynamic biomarkers will be assessed to demonstrate evidence of biologic activity of GDC-9545 in patients and to inform potential revisions to the PK sample collection schedule.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation.

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.3.4.1 Rationale for Changes in Ki67 as Primary Endpoint

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 scores reflect the ability of endocrine agents to suppress proliferation (Dowsett et al. 2005a, 2005b; Ellis et al. 2008). 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 scores was significantly greater 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; hazard ratio = 0.87; 95% CI: 0.78 to 0.97; p = 0.01) and time-to-recurrence (402 vs. 498; hazard ratio = 0.79; 95% CI: 0.70 to 0.90; p = 0.0005), and significantly reduced distant metastasis (324 vs. 375; hazard ratio = 0.86; 95% CI: 0.74 to 0.99; p = 0.04) and contralateral breast cancers (35 vs. 59; 42% reduction, 95% CI: 12% to 62%; p = 0.01) (Baum et al. 2002; Howell et al. 2005; ATAC et al. 2008).

The POETIC study, a Phase III randomized clinical study with approximately 4000 patients with EBC, 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 (IHC) 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. The POETIC study demonstrated that Ki67 levels at baseline and at 2 weeks postoperative were prognostic of outcomes. At 5 years, patients with low Ki67 levels ($<10\%$) at 2 weeks postoperative had a recurrence rate of 8.4%, and patients with high Ki67 ($\geq 10\%$) levels at 2 weeks postoperative had a recurrence rate of 19.6% (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% vs. 39.6% and PFS 6.5 months vs. 5.4 months, respectively) (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 Rationale for the Collection of Plasma Samples for Somatic Tumor Mutation Analysis

There is increasing evidence that circulating-tumor DNA obtained from blood specimens of patients with cancer 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 isolated from plasma using digital polymerase chain reaction, and/or targeted next-generation sequencing (NGS).

3.3.4.3 Rationale for the Collection of Tissue Samples

Tumor tissue samples from the same lesion will be collected pretreatment (archival or fresh), during treatment (fresh), and post-treatment at surgery (fresh). All tumor tissues will be assessed for ER and PgR protein levels, and proliferative index (Ki67).
In addition, tumor tissue will enable assessment of ER pathway activity using RNA analysis of ER target genes (Guan et al. 2019). 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. This approach offers the opportunity to perform molecular subtyping that may inform breast cancer biology and response to

GDC-9545, endocrine therapy, or CDK4/6 inhibition. The collection of tissue samples may also support future diagnostic development.

3.3.5 Rationale for Non-Standard Clinical Outcome Assessments

Cancer treatments, particularly combination therapies, can produce significant symptomatic adverse events. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch 2010; Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting symptomatic information directly from patients can provide a better understanding of treatment characteristics and their effects. To evaluate the tolerability of GDC-9545 plus palbociclib, patients will be asked to report on their experience related to diarrhea, nausea, vomiting, joint pain, hot flush, rash, and fatigue treatment-related symptoms selected from the validated PRO-CTCAE item bank (see Appendix 3). These symptoms were identified as being salient to patients' experience with GDC-9545 and palbociclib on the basis of preliminary safety data for GDC-9545 and published safety data for palbociclib. An item asking about overall side-effect burden will also be included.

To gather additional information about patients' experiences with novel NET combinations in the EBC setting, patients will be asked to report their expectations, feelings about side effects, and satisfaction with treatment via the CTSQ.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 215 postmenopausal women with operable or inoperable, untreated ER-positive, HER2-negative EBC will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Postmenopausal 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 operable or inoperable invasive breast carcinoma, with all of the following characteristics:
  - cT1c (≥ 1.5 cm)– cT4a–c breast cancer at presentation

    Primary tumor must be ≥ 1.5 cm in longest diameter by ultrasound.
  - Measurable disease by ultrasound as defined per mRECIST (see Appendix 4)
  - Patients with multifocal tumors (more than one mass confined to the same quadrant as the primary tumor) if all lesions are sampled and confirmed as ER-positive/HER2-negative invasive breast cancer and at least one lesion is ≥ 1.5 cm in longest diameter by ultrasound

  - Patients with multicentric tumors (multiple tumors involving more than one quadrant) if all discrete lesions are sampled and confirmed as ER-positive/HER2-negative invasive breast cancer and at least one lesion is ≥1.5 cm in longest diameter by ultrasound
- Candidate for neoadjuvant treatment and considered appropriate for endocrine therapy
- Willingness to undergo breast surgery (mastectomy or breast-conserving surgery) after neoadjuvant treatment
- Willingness to provide three mandatory tumor samples (see Section 4.5.10 for tumor tissue sample requirements) as follows:
  - Pretreatment
  - During treatment at Cycle 0 Day 15 (+1 day)
  - Posttreatment (from surgical specimen) or an optional biopsy (if surgery is not possible or delayed; see Section 4.5.10)
- Documented ER-positive tumor in accordance to American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Allison et al. 2020), assessed locally and defined as ≥1% of tumor cells stained positive on the basis of the most recent tumor biopsy
- Documented PgR status (positive or negative) as per local assessment
- Documented HER2-negative tumor in accordance to 2018 ASCO/CAP guidelines (Wolff et al. 2018), assessed locally on the most recent tumor biopsy
- Ki67 score ≥5% analyzed centrally (recommended) or locally (by Sponsor pre-approved assay/scoring method)

  Use of the central laboratory for Ki67 level testing for eligibility is recommended.

  For sites using the central laboratory to test for Ki67 eligibility, a tissue sample must be submitted to the central laboratory for enrollment by the IHC-based central pathology laboratory Ki67 Clinical Trial Assay (see Section 4.5.10 for additional details).
- Postmenopausal status defined as one of the following:
  - Documented bilateral surgical oophorectomy (≥14 days prior to first treatment on Day 1 of Cycle 1 and recovery from surgery to baseline)
  - Age ≥60 years and 12 consecutive months with no menses without an alternative medical cause
  - Age <60 years and ≥12 continuous months of amenorrhea with no identified cause other than menopause, estradiol levels, and follicle-stimulating hormone (FSH) levels in the postmenopausal range
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0–1

- Adequate organ function as defined by the following criteria:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL)
  - AST and serum ALT $\leq 2 \times$ upper limit of normal (ULN)
  - Hemoglobin ≥ 90 g/L (9 g/dL)
  - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert syndrome: $\leq 3 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN or estimated creatinine clearance ≥ 60 mL/min as calculated per institutional guidelines
- INR $< 1.5 \times$ ULN and aPTT $< 1.5 \times$ ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2 and 3 is required.

  For patients receiving heparin, PTT (or aPTT) between 1.5 and $2.5 \times$ ULN (or patient value before starting heparin treatment) is required.

  If anticoagulation therapy is required for a prosthetic heart valve, stable INR between 2.5 and 3.5 is permitted.

4.1.2 Exclusion Criteria

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

- Stage IV (metastatic) breast cancer
- Inflammatory breast cancer (cT4d)
- Bilateral invasive breast cancer
- History of invasive breast cancer
- History of ductal carcinoma in situ or lobular carcinoma in situ if they have received any systemic therapy for treatment or radiation therapy to the ipsilateral breast

  Patients treated with surgery alone may be eligible.
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
- Previous systemic or local treatment for the primary breast cancer currently under investigation (including excisional biopsy or any other surgery of the primary tumor and/or axillary lymph nodes, radiotherapy, cytotoxic, and endocrine treatments)
- History of any prior treatment with AIs, tamoxifen, SERDs, or CDK4/6 inhibitors
- Major surgery within 4 weeks prior to randomization

- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including hepatitis (e.g., hepatitis B virus [HBV] or hepatitis C virus [HCV]), current alcohol abuse, cirrhosis, or positive test for viral hepatitis as defined below:

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

  Patients who test positive for HBcAb are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction is negative for HBV DNA.

  Patients who are positive for HCV serology are only eligible if testing for HCV RNA is negative.
- 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 anastrozole, or palbociclib or any of its excipients
- Known issues with swallowing oral medication
- History of documented hemorrhagic diathesis, coagulopathy, or thromboembolism
- Active cardiac disease or history of cardiac dysfunction including any of the following:
  - History or presence of symptomatic bradycardia or resting heart rate <50 bpm at screening

    Patients on stable dose of a β-blocker or calcium channel antagonist for pre-existing baseline conditions (e.g., hypertension) may be permitted if resting heart is ≥ 50 bpm.
  - History of angina pectoris, symptomatic pericarditis, myocardial infarction, or any cardiac arrhythmias (e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality) within 12 months prior to study entry
  - History of documented congestive heart failure (New York Heart Association Class II–IV) or cardiomyopathy
  - Left ventricular ejection fraction $<50\%$ as determined by multiple-gated acquisition scan or echocardiogram
  - QT interval corrected through use of Fridericia's formula (QTcF) >470 ms based on mean value of triplicate ECGs, history of long or short QT syndrome, Brugada syndrome or known history of corrected QT interval prolongation, or torsades de pointes

  - 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, sick sinus syndrome, or evidence of prior myocardial infarction
  - 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 long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval (see Section 4.4.2.2)
- Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or major upper gastrointestinal (GI) surgery including gastric resection
- Treatment with strong CYP3A4 inhibitors or inducers within 14 days or 5 drug elimination half-lives (whichever is longer) prior to randomization
- Known HIV infection
- Serious infection requiring oral or IV antibiotics, or other clinically significant infection within 14 days prior to screening

  Patients who fully recovered from serious and clinically significant infections within 14 days prior to screening are eligible.
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: experimental arm or control arm. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- cT status: cT1c–cT2 versus cT3–cT4a–c
- Ki67 score: $<20\%$ versus $\geq 20\%$
- PgR status: positive versus negative

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are GDC-9545, anastrozole, and palbociclib.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 GDC-9545

GDC-9545 will be supplied by the Sponsor as 30-mg capsules packaged in high-density polyethylene bottles with a plastic child-resistant cap with induction seal and desiccant. For information on the GDC-9545 formulation, see the pharmacy manual and the GDC-9545 Investigator's Brochure.

4.3.1.2 Anastrozole

Anastrozole will be supplied by the Sponsor as 1-mg film-coated tablets. For information on the anastrozole formulation, see the local prescribing information for anastrozole.

4.3.1.3 Palbociclib

Palbociclib will be supplied by the Sponsor as 75-, 100-, and 125-mg hard gelatin capsules. During the course of the study, the formulation may switch to 75, 100, and 125-mg tablets. For additional information on the palbociclib formulation and packaging, see the local prescribing information for palbociclib.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1 and outlined in Figure 1 and Figure 2.

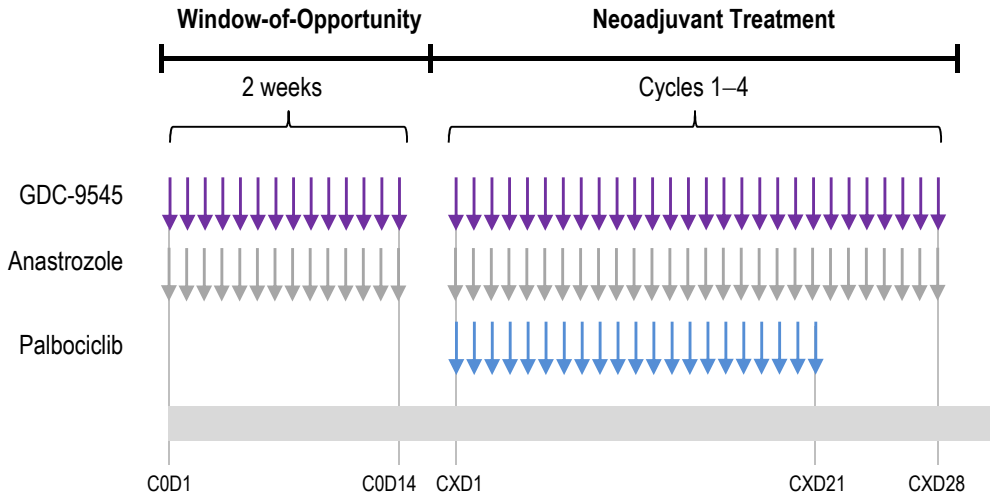
Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

To assess patient compliance with self-administration of study medication (GDC-9545, anastrozole, and palbociclib), site study staff will provide patients with detailed instructions and training for the handling and administration of study drugs. Patients will receive and should be instructed to complete a medication diary. Patients will be instructed to bring all unused study medication and their medication diaries to the clinic at specified study visits (see schedule of activities Appendix 1). Compliance will be assessed by investigator site team staff (e.g., by counting returned tablets/ capsules, clinic visit patient interview notes, and reviewing patient diaries).

Details on treatment administration should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of 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 5.1.4.

Figure 2 Study Treatment Regimens



C = cycle; D = day.

4.3.2.1 GDC-9545, Palbociclib, and Anastrozole

GDC-9545, anastrozole, and palbociclib should be taken orally with food at approximately the same time each day as per study treatment regimen. If palbociclib switches to tablet formation (see Section 4.3.1.3), study treatments may be taken with or without food. The capsule or tablet should be swallowed whole and should not be chewed, crushed, or opened.

During the window-of-opportunity phase, GDC-9545 and anastrozole can be taken with or without food at approximately the same time each day. During the window-of-opportunity phase, starting on Cycle 0 Day 1, GDC-9545 30 mg PO QD or anastrozole 1 mg PO QD will be administered as a single agent for 2 weeks.

During the neoadjuvant treatment phase, GDC-9545 30 mg PO QD or anastrozole 1 mg PO QD will be administered on Days 1–28 of each 28-day cycle in combination with palbociclib 125 mg PO QD on Days 1–21 of each 28-day cycle for four cycles. Starting with Day 1 of Cycle 0 and on Day 1 of each 28-day cycle thereafter, study treatment will be administered in the clinic after the study assessments, as indicated in the schedule of activities (see Appendix 1 and Appendix 2). All other doses will be taken at home on all non-clinic visit days. If a GDC-9545 dose is missed, the dose should be made up unless the next dose is due within 6 hours.

4.3.2.2 Compliance

At the beginning of study participation by a patient, site study staff will provide the patient with detailed instructions and training for the handling and administration of study treatment. Patients will receive and should be instructed to complete a medication diary.

At each clinic visit, the medication diary as well as unused tablets or capsules and all containers or packaging (used or unused) of study treatment should be collected and reviewed for drug accountability.

Treatment compliance will be defined as the number of capsules or tablets taken divided by the expected number of capsules or tablets and reported as a percentage. In case of dose reductions, the expected number of capsules or tablets should reflect the new dose level. Capsules or tablets that are not returned will be considered to have been taken, unless otherwise specified in the patient's diary and/or eCRF. Note that dosing eCRFs should be completed using the following prioritization: 1) site pharmacy drug accountability logs (IMP disbursed minus IMP returned), 2) clinic visit patient interview notes, and 3) patient daily dosing diary.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. 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. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

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 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 accountability log.

Refer to the pharmacy manual and/or the GDC-9545 Investigator's Brochure and the anastrozole and palbociclib local prescribing information for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to GDC-9545

Currently, the Sponsor does not have any plans to provide Roche IMP (GDC-9545) or any other study treatments 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, PROHIBITED FOOD, 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 initiation of study drug to treatment discontinuation or end of study visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

GDC-9545 is primarily glucuronidated via UGT1A4. It is unlikely that any clinically relevant drug-drug interaction (DDI) will occur with GDC-9545 both as a perpetrator and as a victim. Palbociclib is primarily metabolized by CYP3A and sulfotransferase enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A.

4.4.1 Permitted Therapy

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

- Symptomatic anti-emetics and anti-diarrheal therapy may be administered at the investigator's discretion.
- Bone-sparing agents (e.g., bisphosphonates, denosumab for the treatment of osteoporosis/osteopenia) are allowed in the study provided patients are on stable doses for at least 4 weeks prior to randomization.
- Patients can be treated per standard of care except for use of any prohibited therapies.

All concomitant medication and/or therapies should be documented in the patient's eCRF.

4.4.2 Cautionary Therapy

4.4.2.1 CYP3A4 Substrate with a Narrow Therapeutic Index

Co-administration of midazolam (sensitive CYP3A4 substrate) with multiple doses of palbociclib increased the midazolam plasma exposure by 61% in healthy subjects

compared with the administration of midazolam alone. Therefore, the dose of a sensitive CYP3A4 substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) may need to be reduced, as palbociclib may increase its exposure (Ibrance® U.S. Package Insert).

The above list of CYP3A4 sensitive substrates with a narrow therapeutic index is not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the internet reference provided below when determining whether a medication is a sensitive CYP3A4 substrate with a narrow therapeutic index and can be safely administered with palbociclib. Palbociclib local prescribing information should also be consulted for information on prohibited therapies and recommended dose adjustments for concomitant medications.
In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

4.4.2.2 Medications Associated with QT Interval Prolongation

Any concomitant medications known to affect QT interval duration, including, but not limited to, the following drugs and drug classes should be used with caution and an alternative therapy should be used when possible: fluoroquinolones, antifungals (i.e., ketoconazole, itraconazole, and fluconazo le), antimalarials, amiodarone, cisapride, clarithromycin, erythromycin, methadone, amitriptyline, maprotiline, clomipramine, citalopram, escitalopram, venlafaxine, quinidine, and Class 1 and 3 antiarrhythmics.

Investigators should use medical judgement and exercise caution when considering the co-administration of drugs known to cause decrease in heart rate in patients already receiving treatment with GDC-9545, and an alternative therapy should be used when possible.

Medications Associated with Bradycardia

Investigators should use medical judgment and exercise caution when considering initiation of concomitant medication known to cause decreases in heart rate including, but not limited to, β-blockers and calcium channel antagonists. An alternative therapy should be used when possible. Patients on a stable dose of a β-blocker or calcium channel antagonist for preexisting baseline conditions (e.g., hypertension) should be monitored closely in case dose modification is warranted.

4.4.2.3 Herbal Therapies

Concomitant use of herbal therapies, especially St. John's wort (strong CYP3A inducer), in combination with palbociclib is not recommended because their pharmacokinetics, safety profiles, and potential DDIs are generally unknown. However, other herbal

therapies (excluding St. John's wort) not intended for the treatment of cancer may be used during the study at the discretion of the investigator and must be reported as concomitant therapy in the eCRF.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited during study treatment as described below:

- Strong CYP3A4 inhibitors, including, but not limited to, the following: atazanavir, ritonavir, lopinavir, telaprevir, telithomycin, indinavir, nelfinavir, saquinavir, clarithromycin, troleandomycin, itraconazole, ketoconazole, voriconazole, posaconazole, conivaptan, diltiazem, nefazodone, and mibefradil

  If co-administration of palbociclib with a strong CYP3A4 inhibitor cannot be avoided, reduce the dose of palbociclib as per palbociclib local prescribing information.

- Strong CYP3A4 inducers, including, but not limited to, the following: rifampin, carbamazepine, phenytoin, enzalutamide, oxcarbazepine, phenobarbital, nevirapine, hyperforin (St. John's Wort), and cyproterone

The above lists of CYP3A4 concomitant medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the internet reference provided below when determining whether a certain medication strongly inhibits or induces CYP3A4. Palbociclib and anastrozole local prescribing information should also be consulted for information on prohibited therapies and recommended dose adjustments for concomitant medications. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

- Investigational therapy (other than protocol-mandated study treatment) is prohibited during study treatment.
- Any concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, biologic therapy, or radiotherapy) is prohibited until after the end of study visit. Adjuvant endocrine therapy may be used after surgery at the investigator's discretion. Adjuvant chemotherapy, if indicated, may be initiated after the completion of the mandatory end-of-study visit.
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate, oral contraception, hormone-eluting intrauterine devices, Gonadotropin-releasing hormone (GnRH) agonists and selective ER modulators (e.g., raloxifene) are prohibited until after the end of study visit.

- Primary prophylactic use of hematopoietic growth factors (e.g., erythropoietins, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor) is not permitted; however, they may be used to treat treatment-emergent neutropenia or anemia as indicated by the current ASCO guidelines or as secondary prophylaxis if dose reduction or delay is not considered a reasonable alternative and with approval of the Medical Monitor.

Enrolled patients who subsequently require the use of any prohibited therapies must be discontinued from study treatment as outlined in Section 4.6.1.

4.4.4 Prohibited Food

Use of the following foods is prohibited as described below:

- Consumption of grapefruit, grapefruit juice, grapefruit supplements, or Seville oranges (potent CYP3A4 enzyme inhibitors) is prohibited for at least 3 days prior to initiation of study treatment and during study treatment.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 and Appendix 2. 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 toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

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. Patients who do not initially meet all eligibility criteria, other than HR status and Ki67 score, may be re-screened once at the investigator's discretion.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including tumor size, tumor grade, nodal status, and ER/PgR/Ki67 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, as allowed by the local regulations.

4.5.3 Additional Restrictions

No food or fluids other than water will be allowed from 8 hours prior to the lipid panel test at screening and end of study visit.

4.5.4 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, GI, and neurologic systems. Bilateral breast examination including evaluation of local-regional lymphatics should be conducted as per Section 4.5.6. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed, physical examinations should be performed at specified post-baseline visits and as clinically indicated. 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.

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. 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 (see Section 5.3.5.5).

4.5.6 Local-Regional Tumor Status

Assessment of primary tumor and regional lymph nodes must be performed by physical examination. Physical examination of breast and axilla will be mandatory at screening and prior to each cycle of neoadjuvant therapy, as indicated in Appendix 1.

4.5.7 Tumor and Response Evaluations

Before starting neoadjuvant treatment, the primary tumor site must be marked using a method that is routine clinical practice (e.g., skin tattoo or surgical clip) to enable appropriate surgical excision in case of tumor regression during neoadjuvant therapy.

Tumor response will be evaluated with ultrasound. Breast ultrasounds will be mandatory at screening (within 28 days prior to randomization) and after final dose of neoadjuvant combination treatment (i.e., after Cycle 4 Day 21 and prior to surgery; see Appendix 1). If with ultrasound examination at baseline there is evidence of suspicious axillary lymph

nodes, then fine-needle aspiration or core biopsy is required. Sonographic tumor measurements are to be recorded in the eCRF. Response assessments will be made by the investigator on the basis of ultrasound through use of mRECIST (see Appendix 4). Confirmation of response will not be required.

At the investigator's discretion, assessments may be repeated at any time if progressive disease is suspected.

4.5.8 Tumor Staging

Baseline distant site tumor staging procedures are not mandatory and should be performed as per local practice, in alignment with national guidelines and as clinically indicated, within 28 days prior to randomization.

For reference, per National Comprehensive Cancer Network guidelines, staging procedures are based on clinical stage as follows:

- Stages IIA–IIB: Bone scan is to be performed in presence of bone pain and/or elevated ALP; abdominal/pelvic PET/computed tomography (CT) scan in case of elevated ALP, abnormal liver function tests, abdominal symptoms, or abnormal physical examination; and chest PET/CT scan if pulmonary symptoms are present.
- Stages IIIA–IIIC: Bone scan and PET/CT scan of chest, abdomen, and pelvis is to be performed; liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease.

4.5.9 ECOG Performance Status

Performance status will be completed at screening and as specified in the schedule of activities (see Appendix 1) using the ECOG Performance Status Scale (see Appendix 5) and recorded on the eCRF.

4.5.10 Ki67 Assessment

Biological response to the study treatment will be assessed by measuring changes in cell proliferation (Ki67 protein levels) using formalin-fixed, paraffin-embedded core (FFPE) histopathology sections of the tumor biopsy specimens collected at the following timepoints:

- **Screening, prior to initiation of treatment.** A representative FFPE tumor specimen from a primary breast tumor (not lymph nodes) in a paraffin block is preferred, or at least 15–20 slides containing unstained, freshly cut, serial tissue sections should be submitted along with an associated de-identified pathology report prior to study enrollment. Regardless if Ki67 testing to determine eligibility is performed by central or local laboratory, a tissue sample must be submitted to the central laboratory. For sites using the central laboratory for Ki67 testing of eligibility, a tissue sample must be submitted to the central laboratory for enrollment by the IHC-based central pathology laboratory Ki67 Clinical Trial Assay. If local Ki67 testing of tumor tissue for eligibility is strongly preferred by a site, this may be permitted only if testing will be performed using a Sponsor pre-approved IHC-based assay and

scoring method. Sponsor approval is required before any local testing of Ki67 for eligibility is permitted. If Sponsor-approved local Ki67 testing is used to determine eligibility and stratification, confirmation of shipment of the pretreatment tumor tissue sample to the central pathology laboratory is required prior to randomization. If the central Ki67 result becomes available prior to a patient's randomization, the site must defer to the central result to determine eligibility even if the approved local result determines otherwise. If a high level of discordance is observed between the eligibility determined by the local Ki67 results and the central pathology laboratory results determined after randomization, the Sponsor may discontinue the use of local testing at a site or at study level for the purposes of determining eligibility.

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

Archival tumor tissue from prior diagnostic FFPE cores may be used; however, if archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment fresh tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria. If a pretreatment tumor biopsy is determined to be required, two FFPE core-needle biopsies embedded in a single paraffin block and one freshly frozen optimal cutting temperature (OCT) core-needle biopsy will be required.

- **After 2 weeks of treatment and at the time of surgery.** FFPE and non-FFPE samples will be prepared from the newly collected tumor biopsies and surgical resection.

  Two FFPE core-needle biopsies embedded in a single paraffin block and one freshly frozen OCT core-needle biopsy are required on Day 15 (+1 day).

  For the post-treatment tissue sample collected at surgery, an FFPE tumor block from surgical resection 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 15–20 paraffin embedded, unstained slides from the surgical specimen are required. A freshly frozen OCT tumor tissue sample at surgery is required, unless not clinically feasible.

  If the patient has pCR at time of surgery, tumor surgical specimens will no longer required.

All tumor tissue samples collected during the study will be sent to one or several central laboratories or to the Sponsor or a designee for analysis.

A detailed description of tissue quality requirements and procedures for collection, handling and shipping of tumor tissue samples will be provided in a separate laboratory manual.

4.5.11 Surgical Treatment Plan

Patients will be scheduled to undergo surgery after four cycles of neoadjuvant therapy. Surgery must take place within a maximum of 14 days after the last cycle in the neoadjuvant treatment phase and ideally as soon as possible after the last dose of study treatment. Patients may undergo breast-conserving surgery or mastectomy in accordance to routine clinical practice, and the procedure should be documented and reported in the eCRF.

Sentinel lymph node biopsy is not allowed prior to neoadjuvant therapy. Surgical management options for axillary lymph nodes include sentinel lymph node biopsy (after neoadjuvant treatment) and axillary lymph node dissection of Level I and II lymphatics at the moment of breast surgery. The choice of the axillary procedure will be based on the clinical status of axilla, T stage, and local practice.

4.5.12 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples should be collected according to the schedule of activities (see Appendix 1 and Appendix 2). Results of the following assessments should be available for review at each clinic visit (as required per the schedule of activities) prior to dosing to inform dosing decisions: complete blood count with differential, total bilirubin, ALP, AST, ALT, creatinine, and BUN/urea.

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, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH
- Fasting lipid panel: cholesterol, HDL, LDL, and triglycerides
- Coagulation: INR, aPTT, and PT
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria)

- HBV serology: HBsAg, HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- FSH, for patients $<$60 years
- Estradiol, for patients $<$60 years

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis (see Appendix 2), unless otherwise indicated:

- Plasma samples for PK analysis
- Blood and plasma samples for exploratory research on biomarkers and biomarker assay development
- Archival (diagnostic) or newly collected tissue sample obtained prior to initiation of treatment for determination of baseline Ki67 scores and for exploratory research on biomarkers and biomarker assay development (see Section 4.5.10 for tumor tissue sample requirements)
- Mandatory tumor tissue samples obtained on Day 15 (+1 day) after single-agent treatment and at the time of surgery to evaluate changes in Ki67 scores and for exploratory research on biomarkers and biomarker assay development (see Section 4.5.10 for tumor tissue sample requirements)

Tumor tissue specimens may be used for centralized retrospective assessment to evaluate correlation between genes, proteins, DNA, and RNA relevant to the signaling pathways and sensitivity/resistance to the investigational agents.

Exploratory biomarker research may include, but will not be limited to, analysis of expression of *ESR1* and ER target genes, signatures associated with breast cancer subtypes, immune-related genes, and PI3K signaling genes. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of gene and/or protein expression; analysis of mutations, copy number, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. DNA extracted from blood and plasma may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. NGS methods may include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, but only at participating sites (see Section 4.5.15).

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 4.5.17), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Blood, plasma, and tumor tissue samples collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed or earlier depending on local regulations.
- Plasma samples collected for PK analysis may be needed for additional pharmacokinetics and its associated biomarker characterization and for PK assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or by 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 no later than 6 weeks 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 genomic variants, 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.

4.5.13 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and 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. Twelve-lead single 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 post-dose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. 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 5.1.4. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.14 Clinical Outcome Assessments

PRO data will be collected to more fully characterize the clinical profile of GDC-9545 plus palbociclib compared with anastrozole plus palbociclib in patients enrolled in the study. PRO data will be collected at the clinic sites using select items of the PRO-CTCAE and the CTSQ measure in its entirety according to the schedule of assessments (see Appendix 1).

If after completion of the PROs (i.e., PRO-CTCAE) at the start of a treatment cycle it is determined that the dose of palbociclib should be delayed, the PROs will not be re-administered when the patient returns to the clinic following the delay. The timing of subsequent PRO assessments will be based on the actual Day 1 of the given GDC-9545 cycle when palbociclib was administered.

4.5.14.1 Data Collection Methods for Clinical Outcome Assessments

PRO questionnaires, translated into local languages as appropriate, will be distributed by site personnel via paper booklets provided by the Sponsor for self-administration by patients at specified timepoints during the study (see Appendix 1). PROs will be administered at the clinic before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. Following completion, site personnel will enter PRO data into the study database.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.

- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be <5 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

4.5.14.2 Description of Clinical Outcome Assessment Instruments

PRO-CTCAE

The PRO-CTCAE is a validated item bank that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of seven symptoms deemed most applicable to the current treatments has been selected for this study (i.e., diarrhea, nausea, vomiting, fatigue, joint pain, hot flush, and rash; see Appendix 3). Symptoms have been selected on the basis of being self-reportable, having a symptomatic equivalent in the PRO-CTCAE item library, and being associated with GDC-9545 or palbociclib based on preliminary safety or published studies.

An additional question based on item 5 of the Functional Assessment of Cancer Therapy: General instrument will be administered to provide an overall assessment of tolerability (i.e., side effect burden).

Cancer Therapy Satisfaction Questionnaire

The CTSQ (see Appendix 6) is a validated measure used to assess expectations, experience, and satisfaction with cancer treatments (Abetz et al. 2005; Trask et al. 2008). It contains 16 items that are rated on 5-point Likert scales assessing domains regarding

expectations, feelings about side effects, and overall satisfaction. The CTSQ uses a recall period of the last 4 weeks.

4.5.15 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research 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 WGS or WES, this section of the protocol (Section 4.5.15) will not be applicable at that site.

Genomics is increasingly informing researchers' 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 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.

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

Refer to Section 4.5.12 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.16 Optional Tumor Biopsies

Consenting patients will undergo an optional tumor biopsy at screening and/or at end of treatment. At screening, for patients with an acceptable archival tumor tissue specimen, one freshly frozen OCT core-needle biopsy is requested.

If surgery is delayed or if the patient is not operable or will not undergo surgery for other reasons, an optional biopsy may be performed as a separate procedure within 2 days from the end of the combination treatment. If a patient does not complete 16 weeks (four cycles) of combination therapy, an optional biopsy may be performed within 2 days from the end of the combination treatment, either from the surgical specimen, or if surgery is not performed within 2 days after the end of the combination treatment, from a separate biopsy. If an optional biopsy is performed within 2 days after the end of the combination treatment, two FFPE core-needle biopsies embedded in a single paraffin block and one freshly frozen OCT core-needle biopsy are required.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. 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 Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.12. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.12 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.17 Optional Samples for Research Biosample Repository

4.5.17.1 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

4.5.17.2 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 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 4.5.17) will not be applicable at that site.

4.5.17.3 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, serum, plasma, and 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 blood and tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) 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 WGS, 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).

4.5.17.4 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.

4.5.17.5 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.

4.5.17.6 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 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.

4.5.17.7 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
- Intolerable toxicity related to study treatment determined by the investigator to be unacceptable given the potential for treatment benefit and the severity of the event
- Disease progression per investigator's assessment
- Non-compliance with protocol specified drug administration and follow-up tests
- Concomitant use of any other (non-protocol) systemic anti-cancer therapy
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Patients will return to the clinic for an end of study visit 28 (±3) days after the final dose of study drug (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from the Study

Patients will return to the clinic for an end of study visit 28 (±3) days after the final dose of study drug.

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
- Adverse event
- Loss to follow-up
- Progression of the disease
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. 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 not be replaced.

Patients who are withdrawn or withdraw from study participation (and not just study treatment) will not be followed up for any reason after consent has been withdrawn.

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)

4.6.5 Clinical Trial Conduct, in Light of COVID-19 or Other Significant Events with Global Impact

Due to coronavirus disease 2019 (COVID-19) or other significant event with global impact (e.g., pandemic, natural disaster), there are challenges that could affect the conduct of clinical studies. In such situations, the Sponsor will provide further guidance where possible, and investigators will be requested to discuss individual patient considerations with the Medical Monitor.

Prospective protocol waivers remain unacceptable due to COVID-19 or other significant events with global impact. It is critical to ensure that protocol deviations are fully documented, to enable appropriate evaluation of the effect on the clinical study.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

GDC-9545 is not currently approved for any indication, and clinical development is ongoing. Palbociclib has not been approved for patients with ER-positive, HER2-negative early stage breast cancer (see Section 1.5). Anastrozole has been approved for patients with ER-positive early stage breast cancer in the adjuvant setting. The combination of palbociclib plus an AI (anastrozole or letrozole) has been evaluated in neoadjuvant studies showing a favorable safety profile (see Section 1.5). The safety plan for patients in this study is based on clinical experience with palbociclib and AI in published clinical trials and authorized use, and on clinical experience with GDC-9545 in ongoing studies. The anticipated important safety risks and management plan for GDC-9545, are outlined below. Patients should be instructed to promptly contact the investigator if any adverse event develops.

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. Patients will undergo 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 dosage modification and treatment interruption or discontinuation, are provided below.

Refer to the GDC-9545 Investigator's Brochure for a complete summary of safety information. Currently, there is no identified risk with GDC-9545; however, the summary

of potential risks are provided below. Refer to the local prescribing information for a complete summary of safety information for palbociclib and anastrozole.

In addition to these guidelines, more conservative dose modifications of any study treatment for the management of adverse events are permitted at the discretion of the investigator if deemed to be in the best interest of the patient.

5.1.1 Potential Risks Associated with GDC-9545

5.1.1.1 Hepatoxicity

Isolated events of increases in transaminases and bilirubin have been observed with treatment of GDC-9545 at low frequency and primarily at low grades, with a single Grade 3 event of transaminase increase being reported for single-agent GDC-9545 at a dose of 90/100 mg.

In the single-agent study (GO39932) in the GDC-9545 30 mg cohort, only 1 patient experienced a Grade 1 ALT increase, with no other relevant hepatic events reported in other patients at this dose.

Investigators should carefully monitor patients for hepatoxicity following study treatment and follow the recommended management guidelines as noted in Table 2.

5.1.1.2 Gastrointestinal Toxicities

GI effects such as nausea, vomiting, and diarrhea have been reported in association with anti-estrogenic class medications and were also observed in the Phase I study of GDC-9545. Most of these events were low grade in severity and resolved without intervention. Patients who receive treatment with GDC-9545 should be closely monitored for GI effects and any consequent sequelae such as changes in blood chemistry parameters or dehydration. Supportive care should be followed per institutional guidelines.

Investigators should carefully monitor patients for GI effects following study treatment and follow the recommended management guidelines as noted in Table 2.

5.1.1.3 Venous Thromboembolic Events (including Pulmonary Embolism)

Thromboembolic events occur in patients with malignancies, and the risk may be increased by suppression of ER signaling. Patients should be closely monitored for signs and symptoms of thrombosis and instructed to immediately seek medical attention if thrombosis is suspected.

As of 4 September 2019, no thromboembolic events related to GDC-9545 have been reported.

Investigators should carefully monitor patients for thromboembolic events following study treatment and follow the recommended management guidelines as noted in Table 2.

5.1.1.4 Bradycardia

Seven (9.5%) patients who received single-agent GDC-9545 (all treated at 90 mg or higher dose) reported Grade 1 asymptomatic bradycardia/sinus bradycardia. No adverse event of bradycardia was reported at the 30-mg dose. The mean heart rate decrease was approximately 3 bpm at the dose of 30 mg on Cycle 1 Day 15 and stabilized during the treatment. No clinically significant ECG changes, exercise intolerance, or changes in systolic or diastolic blood pressure were reported because of heart rate decrease at the 30 mg dose level. Follow-up data from patients treated at GDC-9545 30 mg with a post-treatment heart rate drop of $\geq$10 bpm or heart rate $<$60 bpm showed complete reversibility upon discontinuation of GDC-9545 treatment.

Single ECGs will be collected routinely during this study (see Section 4.5.13 and Appendix 1). Investigators should use medical judgment and exercise caution when considering the co-administration of drugs known to cause decrease in heart rate and/or bradycardia and/or prolongation of the QT interval and consider using alternative treatment if possible. In patients with pre-existing baseline conditions for which they are already receiving a stable dose of β-blockers or calcium channel antagonists, investigators should carefully monitor patients for worsening of bradycardia following study treatment and follow the recommended management guidelines as noted in Table 2.

5.1.1.5 Renal Toxicity or Increased Creatinine

Based on nonclinical studies, dose-dependent renal toxicity was observed in rats at $\geq$30 mg/kg and in monkeys at $\geq$60 mg/kg, correlating with clinical pathology findings consistent with renal injury. As of 4 September 2019, no cases of acute kidney injury or adverse events of creatinine increase have been reported. No trends of increase in serum creatinine levels were observed in laboratory results to date.

Investigators should carefully monitor patients for renal toxicity or creatinine increase following study treatment and follow the recommended management guidelines as noted in Table 2.

5.1.1.6 Changes in Female Reproductive Organs and Menopausal Symptoms

Based on the anti-estrogenic pharmacological activity of GDC-9545, the following effects are anticipated to occur: loss of muscle and bone, hot flashes, vaginal dryness or discharge, irritation, mood swings, and decreased libido. These symptoms could potentially be more severe than those experienced by typical menopausal patients.

As of 4 September 2019, the following adverse events classified as “reproductive system and breast disorders” have been reported in patients who received single-agent GDC-9545 at 10–250 mg: vulvovaginal dryness, vaginal discharge, and vulvovaginal pruritus (1 patient each [1.4%]); all were Grade 1. Hot flushes (all Grade 1 or 2 in severity) have been reported in 7 patients (9.5%).

Refer to the GDC-9545 Investigator's Brochure for further information.

5.1.1.7 Female Fertility

GDC-9545 has not been tested in male animals or humans.

In nonclinical studies, perturbation and the irreversible arrest of the estrus cycle was observed microscopically in early development. It is unknown whether a longer recovery period in animals would reveal whether the observed perturbation in the estrus cycle is reversible. Refer to the GDC-9545 Investigator's Brochure for further information.

5.1.1.8 Embryofetal Toxicity

On the basis of the anti-estrogenic pharmacological activity of GDC-9545, administration of GDC-9545 during pregnancy is expected to have an adverse effect and poses a risk to the human fetus, including birth defects and miscarriage.

5.1.1.9 Drug-Drug Interactions

Refer to Section 4.4 for further details on DDIs and recommendations regarding concomitant medications.

5.1.2 Risks Associated with Palbociclib

The important risks associated with palbociclib include hematological disorders, particularly neutropenia, interstitial lung disease/pneumonitis, infections, and embryofetal toxicity. Other common adverse reactions include stomatitis, nausea, vomiting and diarrhea, changes in appetite, rash, alopecia, fatigue, pyrexia, and increases in transaminases. Refer to the palbociclib local prescribing information for information on all the risks associated with palbociclib.

5.1.3 Risks Associated with Anastrozole

The important risks associated with anastrozole include ischaemic cardiovascular events, loss of bone mineral density, and increases in cholesterol. Other common adverse reactions include anorexia, increases in cholesterol, somnolence, carpal tunnel syndrome, sensory disturbances, hot flushes, nausea, diarrhea, vomiting, increases in ALT/AST/ALP, rash, alopecia, allergic reactions, osteoporosis, musculoskeletal pain, vaginal dryness/bleeding, and asthenia. Refer to the anastrozole local prescribing information for information on all the risks associated with anastrozole.

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Dose Modifications

Dose Modification for GDC-9545

No dose modification will be permitted for GDC-9545. See Section 5.1.4.3 for further details on management of adverse events.

Dose Modification for Anastrozole

There are no dose modifications for anastrozole. See Section 5.1.3 for further details on management of adverse events.

Dose Modification for Palbociclib

Management of some adverse events may require dose reductions of palbociclib (see Table 1 for the palbociclib dose-reduction schedule). In general, the investigator may consider continuing palbociclib if the observed adverse event is not thought to be palbociclib related.

Table 1 Dose Reductions for Palbociclib

Dose Level	Palbociclib
Starting dose	125 mg
First dose reduction	100 mg
Second dose reduction	75 mg
Third dose reduction	Not permitted

5.1.4.2 Treatment Interruption

Study treatment may be temporarily suspended in patients who experience toxicity considered related to study drug.

In general, decisions on interruption of any of the study treatment components (GDC-9545, anastrozole, and palbociclib) may be made independently of the others; that is, one study treatment component alone may be interrupted for adverse events attributed to that medication without mandatory interruptions of the other study treatment component as outlined below.

- For temporarily interruption of GDC-9545 or anastrozole:
  - If either GDC-9545 or anastrozole is temporarily interrupted because of toxicity, palbociclib may be continued as monotherapy for a maximum of 28 days.
  - If either GDC-9545 or anastrozole is interrupted and cannot be resumed after being withheld for 28 days, the patient should be discontinued from all study treatment as per Section 4.6.1 and scheduled for surgery (see Section 3.1).
- For permanent discontinuation of GDC-9545 or anastrozole:
  - If either GDC-9545 or anastrozole is permanently discontinued for any reason, the patient should be discontinued from all study treatment as per Section 4.6.1 and scheduled for surgery (see Section 3.1).
- For temporarily interruption of palbociclib:
  - If palbociclib is temporarily interrupted because of toxicity, GDC-9545 or anastrozole may be continued until the Cycle 4 in the neoadjuvant phase.

- If palbociclib administration is withheld because of an adverse event on Day 1 of a given cycle, the palbociclib dosing cycle should not begin until the patient is able to resume administration, which will correspond to a delayed Day 1 visit. All subsequent visits in that cycle and future cycles will be based on the new Day 1 visit.

- For permanent discontinuation of palbociclib:
  - If palbociclib is permanently discontinued, GDC-9545 and anastrozole administration may be continued until Cycle 4 in the neoadjuvant phase.

5.1.4.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 2. Additional guidelines are provided in the subsections below.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events Associated with GDC-9545

Event	Action to Be Taken
Elevation of hepatic transaminases	
General guidance	• If patient presents with jaundice, coagulopathy, abdominal pain, or other symptoms suggestive of hepatic toxicity, perform liver function tests with additional evaluation per institutional guidelines. • If hepatic enzymes are elevated with no obvious malignant cause found, consult with hepatologist. • Treat patient with hepatic enzyme elevation according to local standard of care.
Grade 1 or 2	• Continue GDC-9545. • Rule out alternative etiologies (e.g., disease progression, concomitant medications, or biliary obstruction). • Treat patient according to local standard of care.
Grade 3	• Withhold GDC-9545. • Consult with hepatologist. • If event resolves to baseline or below ULN within 28 days, resume GDC-9545 at full dose. • If event does not resolve to baseline or below ULN within 28 days, permanently discontinue GDC-9545.
Grade 4 or meets criteria as defined by Hy's Law (see Section 5.3.5.6)	• Permanently discontinue GDC-9545. • Consult with hepatologist.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events Associated with GDC-9545 (cont.)

Event	Action to Be Taken
Gastrointestinal events (nausea, vomiting, diarrhea)	
General guidance	• Monitor closely for GI symptoms. If patient presents with nausea, vomiting, or diarrhea, manage according to local standard of care, including use of anti-diarrheal agents and supportive care such as hydration and dietary modification as appropriate. • Infectious or alternate etiologies should be ruled out.
Grade 2	• Manage and treat according to local standard of care. • If persistent despite appropriate medical therapy, withhold GDC-9545 until resolution to Grade ≤ 1.
Grade ≥ 3	• Withhold GDC-9545 until event resolves to Grade ≤ 1. • Manage and treat patient according to local standard of care. • Consider consulting with gastroenterologist. • Resume GDC-9545 at full dose once the event resolves to Grade ≤ 1. • If adverse event is recurring and patient cannot tolerate treatment, then permanently discontinue GDC-9545.
Venous thromboembolic events (including pulmonary embolism)	
General guidance	• Advise patient to seek immediate medical attention if they become aware of any symptoms of PE or DVT, such as acute onset of chest pain, shortness of breath, or swelling in extremities.
Grade ≥ 2	• Withhold GDC-9545 until patient is stable. • Manage and treat patient according to local standard of care. • Resume GDC-9545 at full dose once the patient is stable. • Permanently discontinue GDC-9545 for recurrent thromboembolic events.
Bradycardia	
General guidance	• Monitor patient closely for symptomatic bradycardia.
Grade 1	• Continue GDC-9545. • Continue to monitor patient per schedule of activities (see Appendix 1). • If heart rate falls below 40 bpm, withhold GDC 9545 until heart rate returns to > 40 bpm and patient remains asymptomatic.
Grade 2	• Withhold GDC-9545 and consult with cardiologist. • Resume GDC-9545 at full dose once the event improves to Grade ≤ 1 and the heart rate returns to >40 bpm. • For recurrent Grade 2 bradycardia, permanently discontinue GDC-9545.
Grade ≥3	• Permanently discontinue GDC-9545 and consult with cardiologist.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events Associated with GDC-9545 (cont.)

Event	Action to Be Taken
Renal toxicity or increased creatinine	
Grade 1 or 2	• Continue GDC-9545. • Manage patient according to local standard of care.
Grade ≥3	• Permanently discontinue GDC-9545. • Manage patient according to local standard of care. • Consult with nephrologist.
Non-hematologic toxicity	
Grade 1 or 2	• Continue GDC-9545. • Rule out alternative etiologies.
Grade 3	• Withhold GDC-9545 until symptoms resolve to Grade ≤1, and then resume GDC-9545 at full dose.
Grade 4	• Permanently discontinue GDC-9545.

DVT = deep vein thrombosis; GI = gastrointestinal; PE = pulmonary embolism; ULN = upper limit of normal.

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:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Grade ≥3 hepatitis or elevations in AST or ALT
- Grade ≥3 renal toxicity
- Grade ≥2 bradycardia
- Grade ≥2 thromboembolic event

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in 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 final dose of study treatment.

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

Table 3 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 (v5.0), 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 Table 4:

- 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 4 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 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., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating 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 ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 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 solely 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 mRECIST. 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:

- Hospitalization for respite care

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

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 two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The “Accidental overdose” and “Medication error” boxes would need to be checked for both entries.

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO-CTCAE or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms (via PRO-CTCAE) with investigator reports of adverse events. Sites are not expected to review the PRO-CTCAE or other PRO data for adverse events.

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

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)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

Medical Monitor/Emergency Medical Contact: [redacted], M.D., Ph.D. (Primary)

Telephone No.: [redacted]

Mobile Telephone No.:

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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 to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, all serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study treatment. 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 Roche 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 until 28 days after the final study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Only postmenopausal female patients are permitted in the study. Patients will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, 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 the final dose of study treatment), 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 to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and 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 through use of the reference safety information in the documents listed below:

Drug	Document
GDC-9545	GDC-9545 Investigator's Brochure
Palbociclib	Palbociclib Summary of Product Characteristics
Anastrozole	Anastrozole Summary of Product Characteristics

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

Efficacy analyses will consist of all randomized patients, unless specified otherwise. Safety analyses will include all randomized patients who received any amount of study treatment.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size is determined by the primary efficacy endpoint, central assessment Ki67 change from baseline to Week 2 (see details in Section 6.4.1). Approximately 202 patients will need to be randomized in a 1:1 ratio to either the experimental arm (GDC-9545) or control arm (anastrozole) to allow for 80% power to detect an 8% improvement for mean Ki67 change in 2 weeks from −75% in the control arm to −83% in the experimental arm at one-sided 10% level of significance. This target improvement also corresponds to an effect size of 0.3. Based on Cohen's interpretation (Cohen 1988), an effect size of 0.3 represents a small to medium effect and a 21% non-overlap between the two treatment arms.

Patients with missing central Ki67 score at baseline and/or at Week 2 will be excluded from the analysis of the primary efficacy endpoint. For both experimental and control arms, a 6% missing Ki67 rate is assumed. Thus, a total of approximately 215 patients is projected to be enrolled to account for patients with missing Ki67 scores.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, duration, study drug discontinuation, and study discontinuation, as well as reasons for study drug discontinuation and study discontinuation, will be listed and summarized for each treatment arm. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will also be listed and summarized for each treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Evaluation of treatment group comparability between the treatment arms will include demographic summaries, stratification factors, patient treatment history, and other baseline disease characteristics.

Continuous data will be summarized using means, standard deviations, medians, and ranges. Categorical data will be summarized by counts and proportions.

6.4 EFFICACY ANALYSES

Unless specified otherwise, the analysis population for an efficacy analysis will consist of all randomized patients, with patients grouped according to their assigned treatment.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is Ki67score change during the window-of-opportunity phase, defined as the mean change of Ki67 score from baseline to Week 2. Ki67 score will be centrally assessed and measured in percentage score. All Ki67 scores will be log-transformed before analysis, and 0.1 will be added to all raw Ki67 scores before log-transformation to handle zero raw Ki67 scores.

Mean Ki67 change at Week 2 will be summarized in original percentage scale for each arm, and corresponding 95% CI will be calculated by normal approximation. The change in mean Ki67 score between the experimental arm and control arm will be compared through the use of the z-test. Patients with missing central Ki67 scores at baseline and/or Week 2 will be excluded from the analysis.

The analysis of the primary efficacy endpoint will take place when approximately 202 patients have been randomized and have complete central Ki67 scores for the analysis at both baseline and Week 2.

6.4.2 Secondary Efficacy Endpoints

ORR will be defined as the proportion of patients with a CR or PR, as determined by the investigator according to mRECIST (see Appendix 4). The analysis population for ORR will be all randomized patients with measurable disease at baseline. Patients not meeting the criteria for ORR, including patients without any post-baseline tumor assessment, will be considered as non-responders.

An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. ORR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors to be used will be the same as those used for randomization. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution.

CCCA rate is defined as the proportion of patients with centrally measured Ki67 score ≤2.7%. CCCA rate at Week 2 will be summarized. The difference in CCCA rates between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution. Patients with missing central baseline and/or Week 2 corresponding Ki67 score will be excluded from the analysis.

6.4.3 Exploratory Efficacy Endpoints

CCCA rate is defined as the proportion of patients with centrally measured Ki67 scores ≤2.7%. CCCA rate at surgery will be summarized. The difference in CCCA rates between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution. Patients with missing central baseline and/or Week 2 corresponding Ki67 scores will be excluded from the analysis.

pCR rate is defined as the proportion of patients who achieved pCR in breast and axilla (with pCR defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen, and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy [i.e., ypT0/is, ypN0 in the current American Joint Committee on Cancer staging system]) after completion of neo-adjuvant treatment.

The pCR rate will be analyzed using statistical methods similar to those used for ORR.

6.5 SAFETY ANALYSES

All safety analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of study treatment, with patients grouped according to treatment received.

6.5.1 Analyses of Exposure, Adverse Event, Laboratory, and Vital Sign Data

The frequency, nature, and severity of treatment-emergent adverse events, adverse events leading to death, adverse events leading to study drug discontinuation and dose modification, serious adverse events, and adverse events of special interest will be summarized by treatment arm. All deaths will be summarized. Selected laboratory data will be summarized by treatment received and grade compared with baseline, and measurements outside of the normal range will be identified. Relevant vital signs will be presented using summary statistics by treatment received. Drug exposure will also be summarized, including duration of treatment, cumulative dose, and dose intensity.

Treatment-emergent adverse events are defined as adverse events that occur after the first dose of study treatment. Adverse events will be summarized by mapped MedDRA preferred terms and appropriate MedDRA hierarchy. Adverse event severity will be graded according to NCI CTCAE v5.0. Multiple occurrences of the same event will be counted once at the maximum severity.

6.5.2 Exploratory Analyses of Patient-Reported Outcome Data

PRO-CTCAE

PRO-CTCAE analyses will be descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities during the course of the study. The number and percentage of patients who report each symptom and the change from baseline by category (frequency of occurrence, severity, or interference) will be summarized at each assessment timepoint by treatment arm. For items that are rated on a 5-point Likert scale, the maximum post-baseline score and change from baseline will be summarized by treatment arm.

Results from these exploratory analyses will be presented separately from the safety analyses. PRO-CTCAE data will be analyzed at the item level in line with current NCI recommendations for data handling (Basch et al. 2014). Graphical representation of PRO-CTCAE data over time will also be provided. PRO-CTCAE data will be summarized over time. These analyses will also apply to the “overall treatment burden” item. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data.

CTSQ

CTSQ analyses will be descriptive, summarizing means for each domain score (Expectations of Therapy, Feelings about Side Effects, and Satisfaction with Therapy) by treatment arm. The proportions of missing data will also be presented. CTSQ data may also be analyzed in relation to clinical outcomes and PRO-CTCAE scores; item-level responses may be descriptively explored as well.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean plasma concentration of GDC-9545 versus time data will be tabulated and plotted. Additional PK analyses may be conducted as appropriate and reported in a standalone report.

6.7 BIOMARKER ANALYSES

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. Results will be presented in a separate report.

6.8 OPTIONAL INTERIM ANALYSIS

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct an interim efficacy analysis. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by the Sponsor study team personnel who will have full access to unblinded data. Access to treatment assignment information will follow the Sponsor's standard procedures.

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 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 PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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 laws.

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.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. 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 9.7).

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 (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

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 (see Section 9.6).

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 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 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.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor or delegate will provide clinical operations management, data management, and medical monitoring.

Approximately 90 sites globally will participate to enroll approximately 215 patients. Randomization 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.

A Steering Committee (SC) will provide scientific oversight for the trial. Details on the composition and mandate of the SC will be provided in the SC Charter.

9.6 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 details), and redacted Clinical Study Reports and other summary reports will be made available upon request. 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.

9.7 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 [a]	Window of Opportunity [b]		Neoadjuvant Treatment [c]						Surgery [d]	End of Study [e]
Cycle (28-day cycle)		0		1		2		3	4		
Days	–28 to –1	D1	Biopsy [f] D15 (+1 D)	D1 (+3 D)	D15 (±3 D)	D1 (±3 D)	D15 (±3 D)	D1 (±3 D)	D1 (±3 D)		28 D (±3 D)
Informed consent [g]	x										
Demographic data	x										
Medical history and baseline conditions	x										
PRO-CTCAE [h]				x		x		x	x		
CTSQ [h]									x		
Vital signs [i]	x	x		x	x	x	x	x	x	x	x
Weight	x	x		x		x		x	x		x
Height	x										
Complete physical examination [j]	x										x
Limited physical examination [k]				x		x		x	x	x	
Breast and axilla assessment [l]	x	x		x		x		x	x	x	
Tumor staging [m]	x										
ECOG	x			x		x		x	x		x
ECG (12- lead) [n]	x	x		x		x		x	x	x	x
Hematology [o]	x			x	x	x	x	x	x	x	x
Chemistry [p]	x			x	x	x	x	x	x	x	x

Appendix 1: Schedule of Activities

	Screening [a]	Window of Opportunity [b]		Neoadjuvant Treatment [c]						Surgery [d]	End of Study [e]
Cycle (28-day cycle)		0		1		2		3	4		
Days	–28 to –1	D1	Biopsy [f] D15 (+1 D)	D1 (+3 D)	D15 (±3 D)	D1 (±3 D)	D15 (±3 D)	D1 (±3 D)	D1 (±3 D)		28 D (±3 D)
Coagulation (INR, aPTT, PT)	x										x
Fasting lipid panel [q]	x										x
FSH [r]	x										
Estradiol [r]	x										
Urinalysis [s]	x					x		x	x		x
GDC-9545 or anastrozole (QD Days 1–28 of each cycle)		Administered at clinic visits (Day 1 of each cycle); otherwise administered at home.									
Palbociclib administration (QD Days 1–21 of each cycle)				Administered at clinic visits (Day 1 of each cycle); otherwise administered at home.							
Medication diary [t]		Complete when medication is taken at home or at clinic visit.									
Ki67score assessment [u]	x		x							x	
Tumor assessment (ultrasound) [v]	x								x		
Plasma PK samples				See Appendix 2.							
Biomarker samples (blood and tissue)				See Appendix 2.							
Surgical treatment plan [w]										x	
Concomitant medications [x]	x [x]	x [x]	x	x		x		x	x		x
Adverse events [y]	x [y]	x [y]	x	x		x		x	x	x	x [y]

Appendix 1: Schedule of Activities

CTSQ = Cancer Therapy Satisfaction Questionnaire; D = day; ECOG = Eastern Cooperative Oncology Group; FSH = follicle-stimulating hormone; PK = pharmacokinetic; PO = oral; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; QD = once a day.

Notes: On treatment days that coincide with clinic visits, all assessments should be performed prior to dosing unless otherwise specified.

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

[b] Patients will receive either GDC-9545 30 mg PO QD or anastrozole 1 mg PO QD for 2 weeks.

[c] Patients will receive GDC-9545 30 mg PO QD (Days 1–28/cycle) plus palbociclib 125 mg PO QD (Days 1–21/cycle) or anastrozole 1 mg PO QD (Days 1–21/cycle) plus palbociclib 125 mg PO QD (Days 1–21/cycle) for four cycles (16 weeks), for 28 days per cycle. Starting with Day 1 of Cycle 1, and on Day 1 of each 28-day cycle thereafter, study treatment will be administered in the clinic, after the study assessments.

[d] Surgery will be performed within 14 days after the final treatment in the neoadjuvant treatment phase. If surgery is delayed, if the patient is not operable or will not undergo surgery for other reasons, or does not complete 16 weeks (four cycles) of combination therapy, an optional biopsy may be performed as a separate procedure within 2 days from the end of the combination treatment (see Appendix 2).

[e] Patients who complete the study or who discontinue the study prematurely will return to the clinic for an end of study visit 28 (±3) days after the final study treatment.

[f] A fresh post-dose biopsy will be obtained on Day 15 (+1 day). Blood will be collected from the patient, along with additional samples (see Section 4.5.10 and 4.5.12).

[g] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[h] Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment (see Section 4.5.14).

[i] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[j] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

[k] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated.

[l] Assessment of primary tumor and regional lymph nodes must be performed by physical examination at screening and prior to administration of each cycle of study treatment during neoadjuvant therapy (see Section 4.5.6).

[m] Tumor staging procedures are based on routine clinical practice (see Section 4.5.8).

[n] Patients should be resting in a supine position for at least 10 minutes prior to ECG recording. All ECGs will be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws).

[o] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[p] Chemistry panel (serum or plasma) includes, sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH.

[q] Fasting lipid panel will assess cholesterol, HDL, LDL, and triglycerides (after $\geq$ 8 hours of fasting).

[r] Only for patients $<$ 60 years.

[s] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria). Urinalysis should be performed as clinically indicated during study treatment.

[t] Patients will receive a medication diary and should be instructed to complete the medication diary each day immediately after taking their all study medication during each cycle (e.g., Cycles 0–4). The medication diary and unused capsules or tablets in their bottles should be collected and reviewed on Day 1 of each cycle for drug accountability.

[u] For sample biopsy details, refer to Appendix 2 and Section 4.5.10.

[v] Ultrasound should be performed at screening (within 28 days prior to randomization), between Day 21 of Cycle 4 of the neoadjuvant treatment phase and surgery, and as clinically indicated.

[w] See Section 4.5.11.

[x] 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 initiation of study drug until end of study visit.

[y] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

Appendix 2
Schedule of Pharmacokinetic and Biomarker Samples

Visit	Timepoint	Sample Type
Screening (Day −28 to Day −1)	NA	Pre-treatment archival or fresh tumor tissue sample(s) for biomarkers [a]
		Freshly frozen OCT pretreatment tumor tissue sample (optional) [b]
Cycle 0 Day 1 (Window of Opportunity)	Predose	Plasma for biomarkers
		Blood for WGS [c]
	Predose [d]	GDC-9545 PK (plasma)
	3 (+1) hours post-dose	GDC-9545 PK (plasma)
Cycle 0 Day 15 (±1 D) (Biopsy)	Predose [d]	GDC-9545 PK (plasma)
	Postdose [e]	Fresh tumor tissue samples during treatment for biomarkers [e]
		Plasma for biomarkers [e]
Cycle 2 Day 1(±3 days)	Predose [d]	GDC-9545 PK (plasma)
Surgery [f]	NA	Fresh post-treatment tumor tissue samples for biomarkers [g]
		Plasma for biomarkers [f]
End of study visit	28 days after the final dose of study treatment	GDC-9545 PK (plasma)
		Plasma for biomarkers

FFPE = formalin-fixed, paraffin-embedded; NA = not applicable; OCT = optimal cutting temperature; PK = pharmacokinetic; WGS = whole genome sequencing.

[a] See Section 4.5.10 for details on tumor tissue sample requirements.

[b] Optional pretreatment tumor biopsy for patients who have provided written informed consent, have an accepted archival tumor tissue sample, and if collection of tumor biopsy sample is deemed clinically feasible. One freshly frozen OCT core-needle biopsy is requested.

[c] Not applicable for a site that has not been granted approval for WGS.

[d] Same day as treatment administration (within 2 hours before dosing).

[e] During treatment, fresh tumor biopsy sample and plasma for biomarkers should be collected after the last dose of treatment during the window-of-opportunity phase of the study. Tumor biopsy collection must occur prior to entry into the neoadjuvant phase of the study and any palbociclib administration. See Section 4.5.10 for details on tumor tissue sample requirements.

[f] Refer to Appendix 1.

[g] Fresh post-treatment tumor (FFPE and non-FFPE) tissue surgical and plasma samples should be obtained within a maximum of 14 days after the last cycle in the neoadjuvant treatment phase and ideally should occur as soon as possible after the last dose of study treatment. Post-treatment plasma sample for biomarkers should be collected prior to surgery. See Section 4.5.10 for details on tumor tissue sample requirements; see Section 4.5.16 for details on an optional tumor biopsy collected at end of treatment.

Appendix 3
National Cancer Institute Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (NCI PRO-CTCAE) Items

Item Library Version 1.0 English

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ⊗ in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

4.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

5.	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

6.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

7.	In the last 7 days, how OFTEN did you have HOT FLASHES/FLUSHES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HOT FLASHES/FLUSHES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

8.	In the last 7 days, how BOTHERED were you by the side effect(s) of your treatment?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors: Assessment of Response of Neoadjuvant Therapy in Early Breast Cancer

Conventional response criteria may not be ideal for the assessment of response in the setting of neoadjuvant therapy in early breast cancer. Therefore, Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) have been modified to specifically address assessment of primary breast lesions along with axillary lymph node disease, using a range of breast imaging modalities. Selected sections from the RECIST 1.1 [1] are presented below, with modifications and the addition of explanatory text as needed for clarity.

RECIST v1.1		Modified RECIST Early Breast Cancer Neoadjuvant Therapy
Modalities	CT as primary modality, ultrasound not recommended	No CT; primary assessments by ultrasound and clinical examination
Lymph nodes	May be considered target lesions based on size criteria (≥ 15 mm in SAD)	Only axillary lymph nodes assessed; nodes that are considered abnormal on imaging (based on morphological factors including, but not limited to SAD) to be followed as non-target lesions
Possibility of having only non-target disease	Allowed	Not allowed; primary breast lesions must be measurable by ultrasound

CT = computed tomography; RECIST=Response Evaluation Criteria in Solid Tumors; SAD = short axis dimension.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Measurement

Ultrasound and clinical exam will be used to assess response in this protocol, adhering to response criteria as presented in this appendix.

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

Target Lesions

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should lend themselves to reproducible repeated measurements. Up to 2 lesions in the breast may be identified as target lesions. Per this protocol, target lesions must be ≥1.5 cm. A sum of the diameters of all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease. Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither target nor non-target) since they are, by definition, simple cysts. Pathologic axillary lymph nodes are not to be designated at target lesions, and lymph node measurements are not to be included in the sum of diameters (see below for more detail).

Bilateral breast imaging studies should be conducted as per schedule of activities in Appendix 1. Ultrasound must be used to characterize each target lesion at baseline and during the study and all measurement should be recorded in metric notation.

Non-Target Lesions

Non-target lesions may include any other measurable breast lesions not identified as target lesions, as well as truly non-measurable lesions, such as diffuse skin thickening or other lesions not measurable by reproducible imaging techniques.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Axillary lymph nodes are known to vary widely in size, and signs of abnormality in axillary lymph nodes on imaging include other morphological findings often in addition to changes in nodal size. For these reasons, pathologic axillary lymph nodes on imaging should be identified as non-target lesions at baseline. Change in short-axis dimension may be considered in the assessment of pathology, but measurements are not required, and these lesions should be followed qualitatively, as described below at each response assessment timepoint.

Signs of lymph node pathology on imaging include the following:

- Increase in short axis dimension
- Thickened cortex, either diffusely or asymmetrically enlarged
- Thinning, or replaced fatty hilum
- Irregular margins or spiculations
- Rim enhancement
- Decreased echogenicity of cortex
- Perinodal edema

EVALUATION OF RESPONSE

Evaluation of Target Lesions

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

- Complete response (CR): disappearance of all target lesions
- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline
- In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to accurately measure, below measurable limit (BML) should be indicated.

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

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

Evaluation of Non-Target Lesions

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

- CR: disappearance of all non-target lesions

  All lymph nodes must be non-pathologic in appearance
- Non-CR/Non-PD: persistence of one or more non-target lesion(s)
- PD: unequivocal progression of existing non-target lesions.

  For pathologic axillary lymph nodes, this may be based on a combination of morphological factors, including a potential increase in short-axis dimension.

Special Notes on Assessment of Progression of Non-Target Disease

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

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor.

This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a breast lesion may be reported on an ultrasound report as a "new" cystic lesion, which it is not. A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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

Timepoint Response (Overall Response)

Table 1 provides a summary of the overall response status calculation at each protocol-specified timepoint for which a response assessment occurs.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR, or no non-target lesions identified at baseline	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Any except PD	No	PR
SD	Any except PD	No	SD
NE (Any lesion)	Any except PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

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

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “not evaluable” except where there is clear progression in non-target lesions that are assessed.

Special Notes on Response Assessment

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

Appendix 5
Eastern Cooperative Oncology Group Performance Status Scale

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 6
Cancer Therapy Satisfaction Questionnaire

Cancer Therapy Satisfaction Questionnaire
US English

The following pages ask some questions about your cancer therapy (IV/pills). Within this questionnaire, "Cancer therapy (IV/pills)" refers to your current or most recent cancer therapy or cancer pills (including: hormonal therapy, IV therapy, and cancer pills). Please read each question and answer as honestly as you can without the help of anyone. There are no right or wrong answers; the answers should be based on your own personal experiences.

Your Thoughts about Cancer Therapy (IV/pills)

The following statements ask you to share your **thoughts about cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best represents your opinion (check only one box per question).

	In general, **in the last four weeks**, how *often did you feel*:	Always	Most of the time	Some-times	Rarely	Never
1.	That cancer therapy (IV/pills) would help you to return back to a normal life?	☐	☐	☐	☐	☐
2.	That cancer therapy (IV/pills) would get rid of the cancer?	☐	☐	☐	☐	☐
3.	That cancer therapy (IV/pills) would help prevent the cancer from coming back?	☐	☐	☐	☐	☐
4.	That cancer therapy (IV/pills) would stop the cancer from spreading?	☐	☐	☐	☐	☐
5.	That your cancer therapy (IV/pills) limited your daily activities?	☐	☐	☐	☐	☐
6.	Upset about the side effects?	☐	☐	☐	☐	☐
7.	That cancer therapy (IV/pills) was worth taking even with the side effects?	☐	☐	☐	☐	☐
8.	That cancer therapy (IV/pills) would help you live longer?	☐	☐	☐	☐	☐

9. In general, **in the last four weeks**, how often did you think about stopping your cancer therapy (IV/pills)?

☐ Always ☐ Most of the time ☐ Sometimes ☐ Rarely ☐ Never

Satisfaction with Cancer Therapy (IV/pills)

The following statements are about your satisfaction with your **most recent cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best describes your level of satisfaction (check only one box per question).

10. **Overall**, how worthwhile was your cancer therapy (IV/pills)?

☐ Very worthwhile	☐ Quite worthwhile	☐ Moderately worthwhile	☐ A little worthwhile	☐ Not worthwhile at all

11. **Overall,** was taking cancer therapy (IV/pills) as difficult as you expected?

☐ Much more difficult than I thought it would be	☐ Somewhat more difficult than I thought it would be	☐ As difficult as I thought it would be	☐ Somewhat easier than I thought it would be	☐ Much easier than I thought it would be

12. **Overall,** how well did the **benefits** of cancer therapy (IV/pills) meet your expectations?

☐ Much better than my expectations	☐ Somewhat better than my expectations	☐ Met my expectations	☐ Somewhat worse than my expectations	☐ Much worse than my expectations

13. **Overall,** were the **side effects** of cancer therapy (IV/pills) as you expected?

☐ Much better than I expected	☐ Somewhat better than I expected	☐ Exactly as I expected	☐ Somewhat worse than I expected	☐ Much worse than I expected

14. How satisfied were you with the **form** of your cancer therapy (IV/pills)?

☐ Very satisfied	☐ Satisfied	☐ Neither satisfied nor dissatisfied	☐ Dissatisfied	☐ Very dissatisfied

15. **Overall,** how satisfied were you with your most recent cancer therapy (IV/pills)?

☐ Very satisfied	☐ Satisfied	☐ Neither satisfied nor dissatisfied	☐ Dissatisfied	☐ Very dissatisfied

16. Taking everything into consideration, if given the choice again, would you decide to take this cancer therapy treatment?

☐ Yes, definitely	☐ Probably Yes	☐ I don't know	☐ Probably not	☐ Definitely not

Thank you.