PROTOCOL

TITLE:	**A PHASE II, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF GDC-9545 COMPARED WITH PHYSICIAN'S CHOICE OF ENDOCRINE MONOTHERAPY IN PATIENTS WITH PREVIOUSLY TREATED ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	WO42312
STUDY NAME:	acelERA Breast Cancer
VERSION NUMBER:	4
EUDRACT NUMBER:	2020-001984-10
IND NUMBER:	132,673
NCT NUMBER:	NCT04576455
TEST PRODUCT:	GDC-9545 (RO7197597)
MEDICAL MONITOR:	[redacted], PharmD Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic signature and date stamp on the final page of the document.

CONFIDENTIAL

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	See electronic signature and date stamp on the final page of the document
3	09 July 2021
2	21 October 2020
1	15 May 2020

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol WO42312 has been amended to include recent GDC-9545 safety information as per Investigator's Brochure version 6 (IB v6). In addition, Protocol WO42312 has been amended following the results of drug-drug interaction study (GP44001), which showed that giredestrant is a moderately sensitive CYP3A substrate. Changes to the protocol, along with a rationale for each change, are summarized below:

- Clinical and Safety Data has been updated to reflect recent clinical information as per IB v6. Identified and potential safety risks associated with giredestrant have been updated accordingly (Sections 1.2.2, 5.1.1, and 5.1.2).
- Cautionary use of medications associated with QT interval prolongation for patients receiving giredestrant has been removed from Section 4.4.2 based on IB v6 updates, due to the fact that QT prolongation has been formally refuted as a potential risk with giredestrant.
- Moderate CYP3A inducers has been added to cautionary therapy (Section 4.4.2.4), and language added to prohibited therapy and prohibited food (Sections 4.4.3 and 4.4.4) based on the results of study GP44001 showing that giredestrant is a moderately sensitive CYP3A substrate (Section 4.4). Since the study has already completed enrollment, no further updates have been made to the study eligibility criteria. Contraception requirements have been updated to ensure complete washout of GDC-9545, considering its embryo-fetal toxicity (Sections 4.1.1, 4.1.2 and 5.4.3).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.12.6).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol. Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites (Section 5.4.1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- "Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form" was changed to "Clinical Trial Adverse Event/Special Situations Form" throughout the document.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to protocol version 3.0.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted], PharmD, PhD
SPONSOR:	F. Hoffmann-La Roche Ltd

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 PHASE II, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF GDC-9545 COMPARED WITH PHYSICIAN'S CHOICE OF ENDOCRINE MONOTHERAPY IN PATIENTS WITH PREVIOUSLY TREATED ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
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IND NUMBER:	132,673
NCT NUMBER:	NCT04576455
TEST PRODUCT:	GDC-9545 (RO7197597)
PHASE:	II
INDICATION:	Estrogen receptor–positive, HER2-negative locally advanced or metastatic breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of GDC-9545 compared with physician's choice of endocrine monotherapy in patients with previously treated estrogen receptor (ER)–positive, HER2-negative locally advanced or metastatic breast cancer who have received one or two prior lines of systemic therapy in the locally advanced or metastatic setting.
Endocrine monotherapy is defined as either fulvestrant or an aromatase inhibitor. Specific objectives and corresponding endpoints for the study are outlined below.

EFFICACY OBJECTIVES

PRIMARY EFFICACY OBJECTIVE

The primary efficacy objective for this study is to evaluate the efficacy of GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of the following endpoint:

- Progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

SECONDARY EFFICACY OBJECTIVE

The secondary efficacy objective for this study is to evaluate the efficacy of GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of the following endpoints:

- Overall survival (OS), defined as the time from randomization to death from any cause

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1
- Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Clinical benefit rate (CBR), defined as the proportion of patients with stable disease for ≥24 weeks or a CR or PR, as determined by the investigator according to RECIST v1.1
- Investigator-assessed PFS, in subgroups categorized by baseline *ESR1* mutation status
- Time to deterioration (TTD) in pain severity after randomization, defined as the time from randomization to the first documentation of a ≥2-point increase from baseline on the "worst pain" item score from the Brief Pain Inventory–Short Form (BPI-SF)
- TTD in pain presence and interference after randomization, defined as the time from randomization to the first documentation of a ≥10-point increase from baseline in the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 linearly transformed pain scale score
- TTD in physical functioning (PF) after randomization, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-C30 linearly transformed PF scale score
- TTD in role functioning (RF) after randomization, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-C30 linearly transformed RF scale score
- TTD in global health status (GHS) and quality of life (QoL) after randomization, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-C30 linearly transformed GHS/QoL scale score

EXPLORATORY EFFICACY OBJECTIVE

The exploratory efficacy objective for this study is to evaluate the efficacy of GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of the following endpoints:

- Mean scores and mean change from baseline in functional scores (physical, role, cognitive, emotional, and social), GHS/QoL, and disease- and treatment-related symptom scores, as assessed through use of the QLQ-C30 and QLQ-BR23 scales at specified timepoints

Patient interviews will also explore patients' experience of study drug, therapeutic context and disease journey among a subset of patients treated with GDC-9545.

SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0
- 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 compared with physician's choice of endocrine monotherapy 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)

- Overall tolerability (i.e., bother experienced due to side effects of treatment), as assessed through the General Population, Question 5 (GP5) item from the Functional Assessment of Cancer Therapy–General (FACT-G) questionnaire
- Change from baseline in symptomatic treatment toxicities and overall tolerability/side-effect burden, as assessed through use of the PRO-CTCAE and the GP5 item, respectively

PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the GDC-9545 PK profile (±LHRH agonist) 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 GDC-9545 (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to GDC-9545, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of GDC-9545 activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, disease biology, or other biomarker endpoints

HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of the following endpoint:

- Health utility and visual analog scale score of the EQ-5D-5L for pharmacoeconomic modeling at specified timepoints

STUDY DESIGN

DESCRIPTION OF STUDY

This Phase II, randomized, open-label, multicenter study will evaluate the efficacy and safety of GDC-9545 compared with physician's choice of endocrine monotherapy in patients with ER positive, HER2-negative locally advanced or metastatic breast cancer who have received one or two prior lines of systemic therapy in the locally advanced or metastatic setting.

This study will initially enroll approximately 300 patients across all sites in a global enrollment phase. After completion of the global enrollment phase, additional patients may be enrolled in an extended China enrollment phase at sites in mainland China, and/or Taiwan. The global population will include all patients enrolled during the global enrollment phase (including patients enrolled in mainland China, Hong Kong, and/or Taiwan during that phase), and the China subpopulation will include all patients enrolled in mainland China, and/or Taiwan (i.e., during both the global enrollment phase and the extended China enrollment phase).

Eligible patients will be randomly assigned in a 1:1 ratio to either an experimental arm to receive GDC-9545 or a control arm to receive physician's choice of endocrine monotherapy. Patients will be stratified by site of disease, assessed locally (visceral [any lung and/or liver involvement] vs. non-visceral [absence of any lung and/or liver involvement]), prior treatment with cyclin-dependent kinase (CDK)4/6 inhibitor (yes vs. no); and prior treatment with fulvestrant (yes vs. no). The number of premenopausal/perimenopausal patients and male patients enrolled will be limited to approximately 20% of the study population. The cap of 20% has been chosen to ensure that the mix of patients in this study approximates global clinical practice patterns.

Patients who withdraw from the study or who discontinue study treatment will not be replaced. However, patients who withdraw from the study after screening, but before randomization, will be replaced.

Patients may continue to receive study treatment until disease progression or unacceptable toxicity, whichever occurs first. An exception will be made for patients who have developed isolated brain metastases that are treatable with radiation, provided the patients have experienced a PR, CR, or stable disease for ≥ 24 weeks. These patients will be allowed to continue to receive study treatment until systemic progression of disease and/or further progression in the brain.

After the date of randomization, tumor assessments will be performed every 8 weeks for the first 18 months, then every 12 weeks thereafter, with the exception of bone scans, which will be performed every 24 weeks or as clinically indicated.

Efficacy analyses will be based on the local radiologist's or investigator's tumor assessments. Radiographic images, photographs, and clinical information will be sent to a blinded, independent core imaging laboratory to enable a retrospective evaluation of disease response and progression by an Independent Review Committee.

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to NCI CTCAE v5.0. An Internal Monitoring Committee will also provide safety oversight.

NUMBER OF PATIENTS

This study will initially enroll approximately 300 patients across all sites in a global enrollment phase.

TARGET POPULATION

INCLUSION CRITERIA

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- For women: postmenopausal or premenopausal/perimenopausal status, defined as follows:

  Postmenopausal, as defined by at least one of the following criteria:

  – Age ≥ 60 years
  – Age < 60 years and ≥ 12 months of amenorrhea without an alternative medical cause plus follicle-stimulating hormone and plasma estradiol levels within postmenopausal range by local laboratory assessment, in the absence of oral contraceptive pills, hormone replacement therapy, or gonadotropin-releasing hormone agonist or antagonist.
  – Documented bilateral oophorectomy (≥ 14 days prior to first treatment on Day 1 of Cycle 1 and recovery from surgery to baseline)

  Premenopausal or perimenopausal, defined as not meeting the criteria for postmenopausal, and willing to undergo and maintain treatment with approved LHRH-agonist therapy for the duration of study treatment

  LHRH-agonist therapy may be initiated 28 days prior to Day 1 of Cycle 1 (or according to clinical practice for the selected agent). To minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end of the treatment cycle, monthly injections of LHRH agonist are preferred and to be synchronized with Day 1 of each 28-day cycle.
- For men: willing to undergo and maintain treatment with approved LHRH-agonist therapy for the duration of study treatment

  LHRH-agonist therapy may be initiated 28 days prior to Day 1 of Cycle 1 (or according to clinical practice for the selected agent). To minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end

of the treatment cycle, monthly injections of LHRH agonist are preferred and to be synchronized with Day 1 of each 28-day cycle.

- Locally advanced or metastatic adenocarcinoma of the breast, not amenable to treatment with curative intent
- Disease progression after treatment with one or two lines of systemic therapy in the locally advanced or metastatic setting

  One of the prior lines of systemic therapy may have included chemotherapy.

  Patients may not have received more than one prior targeted therapy regimen in the locally advanced or metastatic setting. Targeted therapies may include, but are not limited to CDK4/6 inhibitors, mTOR inhibitors, PI3K inhibitors or PARP inhibitors.

  One of the prior lines of systemic therapy must have included endocrine therapy, which must have been administered continuously for a minimum of 6 months in the locally advanced or metastatic setting prior to disease progression.

  Patients who were intolerant to their last systemic anti-cancer regimen may be considered eligible if all other eligibility criteria are met (including a minimum of 6 months continuous endocrine therapy).

    Intolerance is defined as any treatment-related Grade 4 adverse event, or any treatment-related Grade 2 or 3 adverse event that is unacceptable to the patient and persists despite standard countermeasures. The reason for intolerance must be fully documented.
- Documented ER-positive tumor according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) or ESMO guidelines, assessed locally and defined as $\geq$ 1% of tumor cells stained positive based on the most recent tumor biopsy (or archived tumor sample)

  Patient must be considered appropriate for endocrine therapy.
- Documented HER2-negative tumor assessed locally and defined as meeting criteria according to ASCO/CAP guidelines.
- Confirmed availability of the most recently collected and representative tumor tissue specimen (i.e., archived formalin-fixed paraffin-embedded tissue block [preferred] or 15–20 slides containing unstained, freshly cut, serial sections), Whenever possible, tumor tissue from a metastatic site of disease is preferred, but archival tumor tissue from the primary tumor is acceptable if it is the most recently collected or most suitable for testing.

  If tumor tissue is not available, a newly collected, pre-treatment biopsy will be required for patient participation. In general, a minimum of three cores per block is preferred.

  If the aforementioned minimum tissue requirements cannot be met because of local regulatory requirements, patient may still be eligible for the study and study team is available for advice.
- Measurable disease as defined per RECIST v.1.1 or bone only disease which must have at least one predominantly lytic bone lesion confirmed by computed tomography or magnetic resonance imaging which can be followed.

  Tumor lesions previously irradiated or subjected to other locoregional therapy will be deemed measurable only if disease progression at the treated site after completion of therapy is clearly documented.
- Eastern Cooperative Oncology Group Performance Status 0–1
- Life expectancy of $>$ 6 months
- 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 $\leq 3 \times$ upper limit of normal (ULN)

    For patients with documented liver metastasis: AST and ALT $\leq 5 \times$ ULN

- Hemoglobin ≥ 90 g/L (9 g/dL)

  The blood counts are to meet the specified criteria without transfusion or growth factor support, unless it is clear that the bone marrow function is adequate and that any aberration has a clear and correctable cause, and the correction undertaken.
- 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 (or PT) < 1.5 × ULN and PTT (or aPTT) < 1.5 × ULN (except for patients receiving anticoagulation therapy)

  For patients receiving 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's 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.
- Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE v5.0 Grade ≤ 1 (except alopecia, Grade ≤ 2 peripheral neuropathy, or other toxicities not considered a safety risk for the patient per investigator's judgment)
- For women of childbearing potential: agreement to take precautions as outlined below for each treatment arm:
  - If assigned to the control arm (physician's choice of endocrine monotherapy), agreement to comply with local prescribing guidelines regarding contraception for the chosen endocrine monotherapy
  - If assigned to the GDC-9545 arm: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

    Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of < 1% per year during the treatment period and for 10 days after the final dose of GDC-9545 or for the time period according to local prescribing guidelines. Women must refrain from donating eggs during this same period.

    A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

    For women of childbearing potential, hormonal contraceptive methods are not allowed in this study.

    The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. LHRH agonists are not adequate contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to take precautions as outlined below for each treatment arm:

- If assigned to the control arm (physician's choice of endocrine monotherapy), agreement to comply with local prescribing guidelines regarding contraception for the chosen endocrine monotherapy
- If assigned to the GDC-9545 arm: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for 10 days after the final dose of GDC-9545 or for the time period according to local prescribing guidelines. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 10 days after the final dose of GDC-9545 or for the time period according to local prescribing guidelines to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

  For female partners of male patients, hormonal contraceptive methods supplemented by a barrier method are permitted.

- Ability to comply with the study protocol, in the investigator's judgment
- Willing and able to use an electronic device for PRO data collection
- For patients enrolled in an extended China enrollment phase: current resident of mainland China, or Taiwan, and of Chinese ancestry

EXCLUSION CRITERIA

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

- Prior treatment with a SERD, with the exception of fulvestrant, if fulvestrant treatment was terminated at least 28 days prior to randomization
- Treatment with any investigational therapy within 28 days prior to randomization
- Major surgery, chemotherapy, radiotherapy, or other anti-cancer therapy within 14 days prior to randomization

  Patient must have recovered from any resulting acute toxicity (to Grade 1 or better) prior to randomization.

  Anticipation of need for a major surgical procedure during the course of the study is exclusionary.

- History of any other malignancy other than breast cancer within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I endometrial cancer

  For participants with a history of other non-breast cancers within 5 years from the date of randomization and considered of very low risk of recurrence per investigator's judgment (e.g., papillary thyroid cancer treated with surgery), eligibility is to be discussed with the Sponsor.

- Advanced, symptomatic, visceral spread that is at risk of life-threatening complications in the short term (including massive uncontrolled effusions [pleural, pericardial, peritoneal] or pulmonary lymphangitis)

- Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease
    - Patients with a history of CNS metastases or cord compression are eligible if have been definitively treated with local therapy (e.g., radiotherapy, surgery), are clinically stable, and have not been treated with anticonvulsants or corticosteroids within 2 weeks prior to randomization.
- Active cardiac disease or history of cardiac dysfunction, including any of the following:
    - History (within 2 years of screening) or presence of idiopathic symptomatic bradycardia or resting heart rate $<$ 50 bpm at screening

        Patients on stable dose of a β-blocker or calcium channel antagonist for preexisting baseline conditions (e.g., hypertension) may be eligible if resting heart rate is at least 50 bpm.
    - History of angina pectoris or symptomatic coronary heart disease within 12 months prior to study entry
    - History of documented congestive heart failure (New York Heart Association Class II–IV) or cardiomyopathy
    - QT interval corrected through use of Fridericia's formula $>$ 470 ms, for women, $>$ 450 ms for men, history of long or short QT syndrome, Brugada syndrome or known history of corrected QT interval prolongation, or torsades de pointes
    - 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.
        - Participants with first-degree heart block may be considered for inclusion following consultation with a cardiologist and determination that no additional cardiac risks are present.
        - Patients with history of well-controlled atrial fibrillation are eligible.
    - History (within 12 months) or presence of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as significant structural heart disease (e.g., severe left ventricular systolic dysfunction, restrictive cardiomyopathy, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, moderate to severe valve disease) or family history of long QT syndrome
        - Clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia) should be corrected prior to enrollment.
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis virus (e.g., hepatitis B or hepatitis C), current alcohol abuse, or cirrhosis

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

    Patients that have tested positive for anti-HBc would be eligible if tests for HBsAg and polymerase chain reaction (PCR) are HBV DNA are negative.

    Patients who have been cured of their HCV infection (must have an undetectable viral load i.e., a sustained virologic response for 3 months after completing treatment) are eligible to enroll. Patients that have tested positive for the HCV antibody would be eligible if tests for HCV RNA are negative. If the patient is a carrier of HCV and tests positive for HCV RNA, they would not be considered eligible.

    For patients who have been successfully treated for viral hepatitis, the possibility of re-activation of the virus or reinfection with viral hepatitis should be considered by the Investigator and the overall potential benefits associated with study treatment for the patient should be deemed to exceed the overall risks.

- Known HIV infection
- Active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or major upper gastrointestinal surgery, including gastric resection, potentially affecting enteral absorption
- Serious infection requiring oral or IV antibiotics, or other clinically significant infection, within 14 days prior to randomization. Patients who fully recovered from serious and clinically significant infections within 14 days prior to randomization 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
- Known allergy or hypersensitivity to any of the study drugs or any of their excipients
- For premenopausal/perimenopausal patients or male patients: known hypersensitivity to LHRH agonists
- Pregnant or breastfeeding, or intending to become pregnant during the study or within *10* days after the final dose of GDC-9545, or within the time period specified per local prescribing guidelines after the final dose of physician's choice of endocrine monotherapy

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

END OF STUDY

The end of this study (global phase and potential China extension phase combined) is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or overall survival follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur at least 25 months after the last patient is enrolled in the global study. In addition, the Sponsor may decide to terminate the study at any time.

LENGTH OF STUDY

The total length of the global phase of the study, from screening of the first patient to the end of the study, is expected to be approximately 40 months. In the event enrollment is initiated in a China extension phase, timelines will be extended as applicable

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal products (IMPs) for this study are GDC-9545 and physician's choice of endocrine monotherapy.

Patients will receive open-label study drug as follows, beginning on Day 1 of Cycle 1:

- Patients in the experimental arm will receive GDC-9545 30 mg taken orally once a day on Days 1–28 of each 28-day cycle.
- Patients in the control arm will receive physician's choice of endocrine monotherapy in accordance with local prescribing guidelines.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

The non-IMPs for this study are LHRH agonists.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary efficacy objective for this study is to evaluate the efficacy of GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of investigator-assessed PFS.

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment. The primary analysis of PFS will be conducted when approximately 166 PFS events from both arms are observed.

DETERMINATION OF SAMPLE SIZE

Approximately 300 patients will be enrolled and randomized in a 1:1 ratio to receive either GDC-9545 (experimental arm) or physician's choice of endocrine monotherapy (control arm). The sample size is determined by the primary endpoint, investigator-assessed PFS, comparing the two treatment arms.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AI	aromatase inhibitor
ALT	*alanine aminotransferase*
ASCO	American Society of Clinical Oncology
AST	*aspartate aminotransferase*
BPI-SF	Brief Pain Inventory–Short Form
CCCA	*complete cell cycle arrest*
CBR	clinical benefit rate
CCOD	clinical cutoff date
CDK4/6	cyclin-dependent kinase 4/6
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
DDI	drug-drug interaction
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
ESO-ESMO	European School of Oncology–European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy–General
FDA	Food and Drug Administration
FES	16 α-fluoroestradiol
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle-stimulating hormone
GHS	global health status
GI	gastrointestinal
GP5	General Population, Question 5
HR	hormone receptor
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IHC	immunohistochemistry

Abbreviation	Definition
IM	intramuscular
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LBD	ligand-binding domain
LHRH	luteinizing hormone–releasing hormone
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network®
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PCET	*physician's choice of endocrine therapy*
PD	pharmacodynamic
PET	positron emission tomography
PF	Physical Functioning (scale)
PFS	progression-free survival
PK	pharmacokinetic
PO	by mouth; orally
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Common Terminology Criteria for Adverse Events
QD	once a day
QoL	quality of life
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
RF	Role Functioning (scale)
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease

Abbreviation	Definition
SERD	selective estrogen receptor degrader
TTD	time to deterioration
ULN	upper limit of normal
VAS	visual analogue scale
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON ESTROGEN RECEPTOR–POSITIVE, HER2-NEGATIVE 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). Breast cancer in men is rare; in 2019, less than 1% of new breast cancer diagnoses in the United States occurred in men (American Cancer Society 2019). Hormone receptor (HR)-positive, HER2-negative breast cancer accounts for 60%–70% of all breast cancers.

The role of estrogen in breast cancer etiology and disease progression is well established (Colditz et al. 1995). Modulation of estrogen activity and/or synthesis is the mainstay of therapeutic approaches in patients with estrogen receptor (ER)–positive breast cancer.

Standard-of-care treatment options for patients with ER-positive, HER2-negative locally advanced or metastatic disease include endocrine therapy, endocrine and targeted therapy combinations, or chemotherapy. Chemotherapy is indicated in patients with symptomatic visceral disease or in patients with disease progression after multiple consecutive endocrine therapy regimens. Additionally, guidelines generally recommend that premenopausal women undergo ovarian ablation or suppression and that men be treated using the same approaches as women (Cardoso et al. 2018; NCCN 2020). Current treatments focus on prolonging life and improving or maintaining quality of life.

Despite the effectiveness of available therapies such as ER antagonists (e.g., tamoxifen), aromatase inhibitors (AIs; e.g., anastrozole, letrozole, and exemestane), selective ER degraders (SERDs; e.g., fulvestrant), cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (e.g., abemaciclib, palbociclib, ribociclib), and other targeted agents such as PI3K inhibitors (e.g., alpelisib), many patients ultimately relapse or develop resistance to these agents and therefore require further treatment for optimal disease control. However, growth and survival of the majority of tumors are thought to remain dependent on ER signaling, despite becoming refractory to AIs or tamoxifen; therefore, patients with ER-positive breast cancer can still respond to second- or third-line endocrine treatment after progression on prior therapy (Di Leo et al. 2010; Baselga et al. 2012). Importantly, there is growing evidence that in the endocrine-resistant state, the ER can signal in a ligand-independent manner (Miller et al. 2010; Van Tine et al. 2011). An agent capable of targeting both ligand-dependent and ligand-independent ER signaling has the potential to improve treatment outcomes in patients with ER-positive breast cancer.

ESR1 mutations appear to be a major mechanism of acquired resistance to AIs and are associated with poorer outcomes (Schiavon et al. 2015; Chandarlapaty et al. 2016; Fribbens et al. 2016). The prevalence of *ESR1* mutation ranges from 25%–40% after AI exposure but only in 2%–3% of endocrine therapy-naive patients (Chandarlapaty et al. 2016), illustrating that *ESR1* becomes an important oncogenic driver under AI-selection pressure. Studies have identified mutations in *ESR1* that encode ERα (primarily Y537S and D538G) affecting the ligand-binding domain (LBD) of the ERα (Segal and Dowsett 2014). The Y537S and D538G mutations have been most commonly detected in metastatic breast cancer clinical samples and are hypothesized to contribute to the resistance to AI therapy (Li et al. 2013; Merenbakh-Lamin et al. 2013; Robinson et al. 2013; Toy et al. 2013; Alluri et al. 2014; Jeselsohn et al. 2015; Niu et al. 2015; Schiavon et al. 2015; Chu et al. 2016). In nonclinical models, mutant receptors are able to drive ER-dependent transcription and proliferation in the absence of estrogen, suggesting that LBD-mutant forms of ER are involved in mediating clinical resistance to endocrine therapy (Li et al. 2013; Robinson et al. 2013; Toy et al. 2013; Segal and Dowsett 2014). ER antagonists that are efficacious against these ligand-independent, constitutively active ER–mutated receptors may be of substantial therapeutic benefit.

Notably, circulating free DNA analysis of the SoFEA clinical trial (NCT00253422) showed that postmenopausal patients harboring *ESR1* mutations have an improved progression-free survival (PFS) when treated with fulvestrant as compared with exemestane after disease progression following nonsteroidal AI therapy (hazard ratio = 0.52; p = 0.02) (Fribbens et al. 2016).

SERDs have the potential to block endocrine-dependent and endocrine-independent ER signaling and have been recognized to offer a therapeutic approach to ER-positive metastatic breast cancer. Fulvestrant, a first-generation SERD, binds, blocks, and degrades the ER, leading to inhibition of estrogen signaling through the ER. Fulvestrant has also shown benefit over anastrozole in frontline patients, as demonstrated in the FALCON study (NCT01602380), a Phase III, randomized, double-blind trial that treated de novo patients with HR-positive, locally advanced or metastatic 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.

Although demonstrating clinical benefit, fulvestrant has unfavorable pharmacokinetic (PK) properties, requiring intramuscular (IM) injection. New agents with superior bioavailability, pharmacokinetics, and more potent activity against the ER (including *ESR1* mutations) are warranted.

Notwithstanding the multiple advances in improving the clinical benefit of endocrine therapy, there is a need for new ER-targeting therapies with increased anti-tumor activity to further delay disease progression and/or overcome resistance to the currently available endocrine therapies and ultimately prolong survival in patients with ER-positive, HER2-negative breast cancer.

1.2 BACKGROUND ON GDC-9545

GDC-9545 is a potent, orally bioavailable, small molecule therapeutic agent that is being developed for the treatment of patients with ER-positive breast cancer. GDC-9545 antagonizes the effects of estrogens via competitive binding to the LBD of both wild-type and mutant ER, with nanomolar potency. Upon binding, GDC-9545 induces an inactive conformation to the ER LBD, as measured by displacement of co-activator peptides. In addition to its direct antagonist properties, the mechanism of action of GDC-9545 includes reducing levels of ERα protein through proteasome-mediated degradation. GDC-9545 enables full suppression of ER signaling, which is not achieved by first-generation ER therapeutics 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 ER.

1.2.1 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 IM 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, increasing ER depletion and inhibition of ER transcriptional activity was observed with the increase of doses up to 20 mg/kg, corresponding to clinical exposures of 30 mg. No further depletion or inhibition was observed from further increasing the dose up to 80 mg/kg (corresponding to a 100-mg clinical dose). 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.

1.2.2 Clinical Data

Giredestrant is being assessed in three metastatic breast cancer studies (GO39932, WO42312 and BO41843), in two neoadjuvant studies (GO40987 and WO42133) and in one adjuvant study (GO42784).

Overall, the identified risks of giredestrant include gastrointestinal toxicity (nausea, vomiting, diarrhea), arthralgia, musculoskeletal pain, dizziness, bradycardia, hepatotoxicity, headache, hot flushes, and fatigue. The potential risks of giredestrant include venous thromboembolism, renal dysfunction, menopausal symptoms, infertility and embryofetal toxicity.

Refer to IB v6 for information on clinical studies, on identified and potential risks for giredestrant and risk-mitigation measures, including guidelines for managing adverse events associated with giredestrant.

1.2.2.1 *Study GO39932*

Study GO39932 *is* 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 (with or without [±] 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 (CCOD) of *17 September* 2021, 17*5* patients in Study GO39932 had received treatment as follows: 111 patients had been treated with single-agent GDC-9545 at doses of 10 mg, 30 mg, 90/100 mg, and 250 mg (± LHRH agonist), and 6*4* patients had been treated with GDC-9545 100 mg in combination with palbociclib 125 mg (± LHRH agonist) (given Days 1–21 with 7 days off).

At the CCOD, 47 patients (26.9%) were ongoing in the study (19 patients [17.1%] in the single-agent cohorts and 28 patients [43.8%] in the combination cohort with palbociclib [± LHRH agonist]).

As of the CCOD, of the 111 patients treated with single-agent GDC-9545, the majority of patients enrolled had visceral (65%) and measurable disease (73%) at baseline, and a small proportion (19.5%) had bone-only disease at baseline. Baseline *ESR1* mutation status of wild type or mutant was reported in 50% and 47% of patients, respectively. The remaining patients (3%) had unknown *ESR1*

mutation status. Twenty-three patients (21%) received prior therapy with fulvestrant and 71 patients (64.0%) with a CDK4/6 inhibitor.

Based on the CCOD, clinical benefit, as measured by either radiographic partial response (PR) or at least 6 months of stable disease (SD), was observed at all four single-agent GDC-9545 doses tested. *Clinical benefit was reported in 106/175 patients (60.6%) overall and in 54/111 patients (48.6%) in the single-agent cohorts (doses ranging from 10-250 mg giredestrant [±LHRH agonist]). In the 30 mg single-agent cohort, a clinical benefit was reported in 22/41 patients (53.7%).*

Furthermore, pharmacodynamic (PD) modulation of specified markers ER, progesterone receptor, and Ki67 could not be differentiated by dose as on-treatment changes were similarly observed.

In the safety-evaluable population, giredestrant was well tolerated and the observed safety profile of the combination of giredestrant and palbociclib was consistent with the known safety profile of the individual drugs. No patients experienced dose-limiting toxicities and the MTD was not reached.

1.2.2.2 *Study WO42312*

Study WO42312 (acelERA Breast Cancer) is a Phase II, randomized, open-label multicenter study evaluating the efficacy and safety of giredestrant compared with
physician's choice of endocrine monotherapy (PCET [fulvestrant or an aromatase inhibitor]) in patients with ER-positive, HER2-negative mBC who have received one or two prior lines of systemic therapy in the locally advanced or metastatic setting.
As of the CCOD (18 February 2022) for the primary analysis, of the 303 patients enrolled, 15.2% patients had discontinued from the study and the majority of those remaining had discontinued treatment; median duration of follow-up was 7.89 months.
Study WO42312 did not meet its primary endpoint of investigator-assessed PFS. Giredestrant showed a numerical improvement relative to physician's choice of endocrine therapy (PCET) in terms of PFS hazard ratio of 0.81 (95% CI: 0.60 to 1.10), which was not statistically significant (p =0.1757). Median PFS was similar between both arms: 5.55 months (95% CI: 4.93 to 7.36) with giredestrant and 5.36 months (95% CI%: 3.71 to 5.55) with PCET and PFS benefit was more pronounced in the subset of patients with baseline ESR1 mutations (hazard ratio: 0.60 [95% CI: 0.35 to 1.03]). The OS data were still immature (<10% events). Numerical increases in other secondary endpoints were observed with giredestrant, for both CBR (31.8% vs. 21.1%) and ORR (12.6% vs. 7.2%).

Giredestrant treatment was well tolerated and considered to have comparable safety to PCET. Overall, 84.7% of giredestrant patients experienced at least one adverse event compared to 71.1% in patients treated with PCET. AEs leading to dose modification or interruption occurred in 13.3% of giredestrant patients and 8.6% of PCET patients. Few events led to treatment withdrawal, with 2 (1.3%) in the giredestrant arm and 3 (2%) in the PCET arm.

1.2.2.3 *Study BO41843*

Study BO41843 (persevERA) is a Phase III randomized, double-blind placebo-controlled, multicenter study evaluating the efficacy and safety of giredestrant combined with palbociclib compared with letrozole combined with palbociclib in patients with ER-positive, HER2-negative locally advanced (recurrent or progressed) or mBC.

Approximately 978 patients are expected to be enrolled in the study. Enrollment of Study BO41843 is ongoing and no efficacy data is available at this point. Preliminary safety data for the study is provided in the IB v6 only for overall patients and in an aggregate format and not by study treatment arm since treatment information is not known for this double blinded study.

1.2.2.4 *Study GO40987*

Study GO40987 was a Phase I, open-label, multicenter, preoperative study to assess relative changes in Ki67 levels and to evaluate the pharmacodynamics, pharmacokinetics, safety, and biologic activity of giredestrant in patients with Stage I–III operable ER-positive, HER2-negative untreated breast cancer. All patients provided a pre-treatment and post-treatment tumor tissue sample. Patients received giredestrant for approximately 14 days at one of three treatment cohorts (10, 30, and 100 mg).
Seventy-five patients enrolled in this study, of which sixty-five were efficacy evaluable. As of 25 May 2021, the study has been completed.

The overall post-treatment geometric mean relative Ki67 reduction with giredestrant compared with baseline was 78%. Complete cell cycle arrest (CCCA; Ki67 ≤2.7%) after approximately 2 weeks of treatment with giredestrant was achieved in 56.9% of all tumors. These results were consistent across all three dose levels (10 mg, 30 mg, and 100 mg).

Overall, giredestrant was well tolerated at all dose levels: the majority of adverse events reported were mild (Grade 1) or moderate (Grade 2) in maximum severity and there were no Grade ≥4 adverse events reported in this study. No serious adverse events or Grade ≥3 adverse events were assessed as related to giredestrant by the investigator.
No deaths were reported in the study and no new safety signal were detected.

1.2.2.5 *Study WO42133*

Study WO42133 (coopERA) was a Phase II randomized, open-label, two arm, multicenter study evaluating the efficacy, safety, and pharmacokinetics of giredestrant versus anastrozole (for 14 days in the window-of opportunity phase) and giredestrant plus palbociclib compared with anastrozole plus palbociclib (for 16 weeks in the neoadjuvant phase) in postmenopausal patients with untreated ER-positive and HER2–negative early breast cancer. 221 patients were enrolled in this study, of which 201 were efficacy evaluable.

In this study, the primary endpoint of relative changes in Ki67 scores from baseline to Week 2 for giredestrant versus anastrozole was met. Giredestrant 30 mg showed a statistically superior reduction of Ki67 over anastrozole. The geometric mean of Ki67 reduction after 2 weeks of treatment with giredestrant was –75% (95% confidence interval [CI]: –80% to –70%) and –67% (95% CI: –73% to –59%) with anastrozole (p= 0.043). A greater rate of CCCA was achieved in patients treated with giredestrant (20%) compared with patients treated with anastrozole (13%), demonstrating superior antiproliferative activity of giredestrant over anastrozole.

Giredestrant was well tolerated both as a single agent and in combination with palbociclib.

1.2.2.6 *Study GO42784*

Study GO42784 (lidERA) is a Phase III, global, randomized, open-label, multicenter study evaluating the safety of giredestrant compared with endocrine therapy of physician's choice in participants ER–positive and HER2–negative early breast cancer.

Enrollment of Study GO42784 is ongoing and no efficacy data is available at this point. Preliminary safety data for the study is internally blinded and therefore, is provided only for overall patients and in an aggregate format and not by study treatment arm.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Despite treatment advances in ER-positive, HER2-negative breast cancer, it remains a disease with significant unmet need, particularly after disease progression with first-line therapy. HR-positive tumors represent the most common form of breast cancer, yet despite adjuvant endocrine therapy, a significant proportion of patients (approximately 30%) remain at risk of relapse. With the development of metastatic disease and subsequent treatment with endocrine therapies, most patients develop resistance to endocrine therapy, and the majority of all breast cancer deaths are due to ER-positive disease.

GDC-9545 is a potent, orally bioavailable ERα antagonist and inducer of ERα degradation that competes with estrogens for binding to the ER, with low nanomolar potency; it is being developed for the treatment of patients with ER-positive breast cancer. GDC-9545 has demonstrated robust nonclinical activity in ER-positive breast cancer models of *ESR1*–wild type and *ESR1*–mutation bearing disease. Furthermore, fulvestrant, an approved SERD molecule, when dosed according to a clinically relevant dosing scheme, was less efficacious than GDC-9545 in the assessed xenograft models (see Section 3.3.1). As described in Section 1.2, GDC-9545 was tolerated in safety pharmacology studies.

The proposed Phase II Study WO42312 is designed to demonstrate a statistically significant and clinically meaningful PFS benefit of GDC-9545 compared with physician's choice of endocrine monotherapy (fulvestrant or an AI) for patients with previously treated ER-positive, HER2-negative locally advanced or metastatic breast cancer.

The present study has incorporated key design elements that are critical to an adequate assessment of benefit versus risk for GDC-9545 in a single Phase II pivotal study. These elements include use of a randomized, multicenter, international study with a primary endpoint of investigator-assessed PFS, supported by key secondary endpoints and adequate power and type I error control to allow the demonstration of robust and clinically meaningful improvement in the primary endpoint. The eligibility criteria are designed to minimize potential risks associated with GDC-9545 (see Sections 4.1.1 and 4.1.2). Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. Safety monitoring and risk mitigation strategies, including detailed management guidelines for treatment-related symptoms or potential risks, are described in Section 5.1. The potential safety issues associated with administration of GDC-9545 therapy are expected to be clinically monitorable and manageable.

An Internal Monitoring Committee (IMC) will review cumulative safety data throughout the study as outlined in a separate charter (see further details in Section 3.1.3).

In the setting of the COVID-19 pandemic, patients with comorbidities including those with HR-positive metastatic breast cancer are a more vulnerable population. In some retrospective analysis, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer.

Based on the mechanism of action and the observed clinical safety profile, it is not anticipated that treatment with GDC-9545 will compromise the immune system nor increase the likelihood or the severity of infection with SARS-CoV-2.

There is an increased risk of exposure to SARS-CoV-2 associated with hospital visits. This risk can be minimized by complying with local guidelines and hospital policies. Metastatic cancer is a life-threatening disease, and treatment with GDC-9545 is expected to provide a clinically meaningful improvement in PFS; therefore, the anticipated benefit–risk of this study remains positive in the setting of the COVID-19 pandemic.

Given that the study drug, GDC-9545, is not expected to increase the risk or severity of COVID-19, no specific SARS-CoV-2 safety management guidelines are deemed necessary, and patients should be treated as per institutional standards of care with decisions for interruptions of study drugs taken by the sites based on the severity of the infection. Please also refer to the guidelines provided for GDC-9545 for the management of non-hematological toxicity in Section 5.1.3.3 and the local labels for other study drugs. Patients with serious infection within 14 days prior to randomization are excluded; however, no testing for SARS-CoV-2 is required. Investigational sites will be specifically trained in the reporting of any occurrences of COVID-19, and the safety of patients will continue to be monitored regularly by both the Sponsor and IMC.

At this time, there is insufficient experience with SARS-CoV-2 vaccines to support concrete recommendations concerning the use of SARS-CoV-2 vaccines in patients receiving GDC-9545 or other endocrine therapies for breast cancer. SARS-CoV-2 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a SARS-CoV-2 vaccine should be individualized based on a patient's SARS-CoV-2 infection/complication risk, the general condition of the patient as well as the epidemiology of COVID-19 in the patient's given area or region.

Based on the data available to date regarding adverse reactions reported in patients receiving SARS-CoV-2 vaccines, the risk of serious or severe overlapping toxicities is low. Based on the mechanism of action and current knowledge, it seems unlikely that GDC-9545 might have an impact on SARS-CoV-2 vaccine efficacy or that mRNA (e.g., Pfizer/ BioNTech BNT162b2, Moderna), inactivated (e.g., Sinopharm, Sinovac, Bharat) replication deficient viral vector (e.g., AstraZeneca/Oxford, Johnson and Johnson, Gamaleya) or protein subunit vaccines (e.g., Anhui Zhifei Longcom, FBRI SRC VB Vector) could impact the safety or efficacy of GDC-9545.

Please check the specific label of any vaccine to ensure compatibility prior to use.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of GDC-9545 compared with physician's choice of endocrine monotherapy (as defined below) in patients with previously treated ER-positive, HER2-negative locally advanced or metastatic breast cancer who have received one or two prior lines of systemic therapy in the locally advanced or metastatic setting. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study drug" refers to test product or the comparator assigned to patients (i.e., GDC-9545 or physician's choice of endocrine monotherapy). Endocrine monotherapy is defined as either fulvestrant or an AI. In addition, premenopausal/perimenopausal patients and male patients will receive an LHRH agonist (e.g., goserelin, leuprolide acetate, or triptorelin).

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 physician's choice of endocrine monotherapy on the basis of the following endpoint:

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

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of the following endpoints:

- Overall survival (OS), defined as the time from randomization to death from any cause
- ORR, defined as the proportion of patients with a complete response (CR) or PR on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to RECIST v1.1
- Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- CBR, defined as the proportion of patients with stable disease for $\geq$24 weeks or a CR or PR, as determined by the investigator according to RECIST v1.1
- Investigator-assessed PFS, in subgroups categorized by baseline *ESR1* mutation status

- Time to deterioration (TTD) in pain severity after randomization, defined as the time from randomization to the first documentation of a ≥2-point increase from baseline on the "worst pain" item score from the Brief Pain Inventory–Short Form (BPI-SF)
- TTD in pain presence and interference after randomization, defined as the time from randomization to the first documentation of a ≥10-point increase from baseline in the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 linearly transformed pain scale score
- TTD in Physical Functioning (PF) after randomization, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-C30 linearly transformed PF scale score
- TTD in Role Functioning (RF) after randomization, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-C30 linearly transformed RF scale score
- TTD in global health status (GHS) and quality of life (QoL) after randomization, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-C30 linearly transformed GHS/QoL scale score

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of the following endpoints:

- Mean scores and mean change from baseline in functional scores (physical, role, cognitive, emotional, and social), GHS/QoL, and disease- and treatment-related symptom scores, as assessed through use of the QLQ-C30 and QLQ-BR23 scales at specified timepoints

Patient interviews will also explore patients' experience of study drug, therapeutic context, and disease journey among a subset of patients treated with GDC-9545.

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0
- 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 compared with physician's choice of endocrine monotherapy 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)
- Overall tolerability (i.e., bother experienced due to side effects of treatment), as assessed through the General Population, Question 5 (GP5) item from the Functional Assessment of Cancer Therapy–General (FACT-G) questionnaire
- Change from baseline in symptomatic treatment toxicities and overall tolerability/side-effect burden, as assessed through use of the PRO-CTCAE and the GP5 item, respectively

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the GDC-9545 PK profile (± LHRH agonist) 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 GDC-9545 (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to GDC-9545, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of GDC-9545 activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in blood, plasma, and tumor tissue (listed in Section 4.5.7) and efficacy, safety, PK, disease biology, or other biomarker endpoints

2.5 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with GDC-9545 compared with physician's choice of endocrine monotherapy on the basis of the following endpoint:

- Health utility and visual analog scale (VAS) score of the EQ-5D-5L for pharmacoeconomic modeling at specified timepoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of the Study

This Phase II, randomized, open-label, multicenter study will evaluate the efficacy and safety of GDC-9545 compared with physician's choice of endocrine monotherapy (as defined in Section 2) in patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer who have received one or two prior lines of systemic therapy in the locally advanced or metastatic setting.

One of the prior lines of systemic therapy must have included endocrine therapy, which must have been administered continuously for a minimum of 6 months in the locally advanced or metastatic setting prior to disease progression. Patients who received prior treatment with a SERD will be excluded from this study. An exception will be made for prior treatment with fulvestrant, if fulvestrant treatment was terminated at least 28 days prior to randomization. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

This study will initially enroll approximately 300 patients across all sites in a global enrollment phase. After completion of the global enrollment phase, additional patients may be enrolled in an extended China enrollment phase at sites in mainland China and/or Taiwan. The global population will include all patients enrolled during the global enrollment phase (including patients enrolled in mainland China, Hong Kong, and/or Taiwan during that phase), and the China subpopulation will include all patients enrolled in mainland China and/or Taiwan (i.e., during both the global enrollment phase and the extended China enrollment phase).

Eligible patients will have histologically or cytologically confirmed diagnosis of adenocarcinoma of the breast with evidence of locally advanced or metastatic disease. Patients must have measurable disease as per RECIST v.1.1 or evaluable bone disease. Adequate archival or fresh tumor tissue availability is required for patient participation.

Eligible patients will be randomly assigned in a 1:1 ratio to either an experimental arm to receive GDC-9545 or a control arm to receive physician's choice of endocrine monotherapy (as defined in Section 2). Patients will be stratified by site of disease, assessed locally (visceral [any lung and/or liver involvement] vs. non-visceral [absence of any lung and/or liver involvement]), prior treatment with CDK4/6 inhibitor (yes vs. no); and prior treatment with fulvestrant (yes vs. no).

The number of premenopausal/perimenopausal patients and male patients enrolled will be limited to approximately 20% of the study population. The cap of 20% has been chosen to ensure that the mix of patients in this study approximates global clinical practice patterns.

Patients will receive open-label study drug as follows, beginning on Day 1 of Cycle 1:

- Patients in the experimental arm will receive GDC-9545 30 mg taken orally (PO) QD on Days 1–28 of each 28-day cycle
- Patients in the control arm will receive physician's choice of endocrine monotherapy in accordance with local prescribing guidelines

In addition, premenopausal/perimenopausal patients and male patients in both arms will receive an LHRH agonist. To minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end of the treatment cycle, monthly injections of LHRH agonist are preferred and to be synchronized with Day 1 of each 28-day cycle (or according to clinical practice for the selected agent).

Crossover between treatment arms will not be permitted in the study.

Patients who withdraw from the study or who discontinue study treatment will not be replaced. However, patients who withdraw from the study after screening, but before randomization, will be replaced.

Patients may continue to receive study treatment until disease progression or unacceptable toxicity, whichever occurs first. An exception will be made for patients who have developed isolated brain metastases that are treatable with radiation, provided the patients have experienced a PR, CR, or SD for ≥24 weeks. These patients will be allowed to continue to receive study treatment until systemic progression of disease and/or further progression in the brain.

Patients will be followed for safety for 30 days after the final dose of study treatment, including a treatment discontinuation visit at 30 days after the final dose (unless final dose resulted in a dose delay prior to decision to discontinue). For the control arm, the upper limit of the visit window will be dependent upon maximum dosing delay as permitted per local guidelines. Thereafter, information on survival and new anti-cancer therapy will be collected every 6 months until death (unless the patient withdraws consent or the Sponsor terminates the study). The survival follow-up period for patients remaining in the study will conclude at the time of the final OS analysis.

After the date of randomization, tumor assessments will be performed every 8 weeks for the first 18 months, then every 12 weeks thereafter, with the

exception of bone scans, which will be performed every 24 weeks or as clinically indicated (see Section 4.5.6.2 for detailed information).

Efficacy analyses will be based on the local radiologist's or investigator's tumor assessments. Radiographic images, photographs, and clinical information will be sent to a blinded, independent core imaging laboratory to enable a retrospective evaluation of disease response and progression by an Independent Review Committee (IRC) (see Section 3.1.2).

To evaluate the PK properties of GDC-9545, sparse PK samples will be collected at various timepoints before and after dosing from all patients in the GDC-9545 arm; a subset of patients in the GDC-9545 arm will be enrolled for intensive GDC-9545 PK sampling (see Appendix 2).

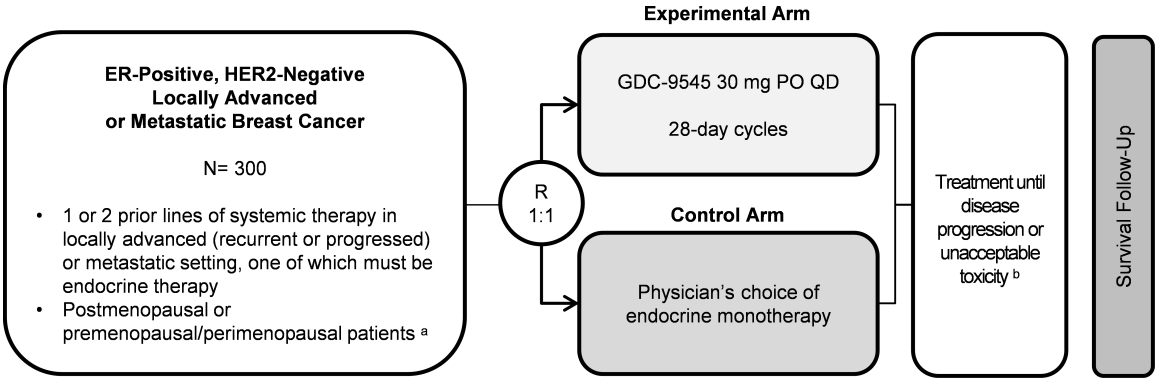
Patient-reported outcome (PRO) instruments will be completed by patients to evaluate the treatment impact from the patient's perspective.

Optional patient interviews will be performed among a subset (up to 30) of patients receiving GDC-9545, to explore patients' experience of study drug, therapeutic context, and disease journey.

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to NCI CTCAE v5.0. An IMC will also provide safety oversight as outlined in Section 3.1.3.

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

Figure 1 Study Schema



ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; LHRH = luteinizing hormone-releasing hormone; PO = orally; QD=once a day; R = randomization.

[a] Premenopausal/perimenopausal patients and male patients in both arms will receive an LHRH agonist. To minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end of the treatment cycle, monthly injections of LHRH agonist are preferred and to be synchronized with Day 1 of each 28-day cycle (or according to clinical practice for the selected agent).

[b] An exception will be made for patients who have developed isolated brain metastases that are treatable with radiation, provided the patients have experienced a partial response, complete response, or stable disease for ≥ 24 weeks (see Section 4.4.3).

3.1.2 Independent Review Committee

All radiological data (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan), photographs of skin lesions, and any additional clinical information required will be sent to a blinded, independent, core imaging laboratory (contracted by the Sponsor) to facilitate a retrospective evaluation of disease response and progression by an IRC. Details about IRC membership and procedures (e.g., tumor assessments) will be outlined in a separate IRC Charter.

3.1.3 Internal Monitoring Committee

An IMC will provide additional safety oversight throughout the study. The IMC will include representatives from Clinical Science, Safety Science, and Biostatistics. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and vital sign and laboratory abnormalities performed by the Medical Monitor, the IMC will periodically review cumulative data during the study. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in the IMC Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study (global phase and potential China extension phase combined) is defined as the date when the last patient, last visit occurs or the

date at which the last data point required for statistical analysis or overall survival follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur at least 25 months after the last patient is enrolled in the global study. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the global phase of the study, from screening of the first patient to the end of the study, is expected to be approximately 40 months. In the event enrollment is initiated in a China extension phase, timelines will be extended as applicable.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for GDC-9545 Dose and Schedule

This study will evaluate GDC-9545 30 mg PO QD administered on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1.

The Phase Ia/Ib study GO39932 evaluated escalating doses of GDC-9545 from 10 to 250 mg PO QD (see Section 1.2.2). 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 events, except for Grade 1 asymptomatic bradycardia/heart rate decrease that was dose-related. No adverse events of bradycardia were reported with doses $<$90 mg. No Grade $\geq$3 bradycardia adverse events have been reported at any dose level up to 250 mg. Indeed, with the exception of one Grade 2 adverse event; all bradycardia adverse events have been Grade 1 in maximum intensity, and no dose reductions have been necessary at any dose level.

Nonclinical 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 approximately 10-fold higher than the steady-state exposure of fulvestrant 500 mg IM monthly, with higher in vitro potency. F-18 16 α-fluoroestradiol–positron emission tomography (PET) showed $>$90% suppression of FES uptake to background levels at 10–250 mg PO QD, regardless of *ESR1* mutation status, indicating target saturation across all dose levels. Clinical activity as measured by CBR was approximately 50% at 30 mg QD. No evidence of additional benefit was observed at doses above 30 mg.

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

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

3.3.2 Rationale for Patient Population

The target patient population for this study is women and men with ER-positive, HER2-negative locally advanced or metastatic breast cancer who have received one or two prior lines of systemic therapy in the locally advanced or metastatic setting.

Endocrine therapies are the mainstay of treatment for HR-positive breast cancer, but many patients relapse during endocrine therapy, which ultimately limits the use of these agents. However, tumors continue to depend on ER activity for growth, and ER remains an important target in the endocrine-resistant setting, emphasizing the need for more effective endocrine treatment. Patients previously treated with fulvestrant are eligible for this study, given that GDC-9545 was more efficacious than fulvestrant in xenograft models of ER-positive breast cancer, when dosed according to a clinically relevant dosing scheme. Furthermore, as of the CCOD of 31 January 2021 in Study GO39932, clinical benefit (confirmed CR, PR, or the first occurrence of PD on or after 24 weeks) was observed for 8 of 26 (30.8%) clinical benefit-evaluable patients treated with single-agent GDC-9545 at various dose levels after prior treatment with fulvestrant.

Hence, the patient population defined by the eligibility criteria reflects patients for whom there is an unmet medical need, as the current standard of care treatment options are limited.

Both postmenopausal and premenopausal/perimenopausal women will be included in the study. Premenopausal/perimenopausal women will receive an LHRH agonist for ovarian function suppression. Male patients will also receive an LHRH agonist.

3.3.3 Rationale for Control Group

Patients with HR-positive recurrent or metastatic breast cancer who respond to an endocrine treatment should receive additional endocrine therapy at disease progression (Cardoso et al. 2018; Thill et al. 2109; NCCN 2020). After first-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy, but many premenopausal and postmenopausal patients with HR-positive breast cancer still benefit from sequential use of endocrine therapies at disease progression. Additional endocrine therapies for second-line and subsequent therapies for postmenopausal women with ER-positive recurrent or progressed metastatic breast cancer typically include nonsteroidal AIs (e.g., anastrozole, letrozole), steroidal AIs (e.g., exemestane), ER antagonists (tamoxifen or toremifene), or SERDs (e.g., fulvestrant). In premenopausal women who received a prior endocrine therapy, the preferred treatment includes ovarian ablation or

suppression, followed by endocrine therapy. The third-generation AIs (i.e., anastrozole, letrozole, and exemestane) have shown superiority to tamoxifen in the metastatic breast cancer setting as well as in the adjuvant setting.

Fulvestrant is clinically effective in patients with ER-positive breast cancer, both in patients naive to and resistant to endocrine therapy. In the first-line setting, fulvestrant is more efficacious than AIs in patients naive to endocrine therapy, both in terms of PFS and OS (FIRST study [NCT00274469]; Ellis et al. 2015) and of PFS (FALCON study [NCT01602380]; Robertson et al. 2016). Fulvestrant has been shown to be effective in patients who have disease progression after receiving tamoxifen. Fulvestrant is also effective after previous treatment with third-generation AIs. Hence, fulvestrant is generally reserved for second-line patients or those first-line patients recurring during or soon after treatment with adjuvant AIs (Robertson et al. 2009; Di Leo et al. 2010). Recently, several new combination therapies with novel agents have become available as second-line and subsequent therapies, such as exemestane with everolimus (Baselga et al. 2012; Yardley et al. 2013) or palbociclib with fulvestrant (Cristofanilli et al. 2016).

In this study, the experimental arm consists of single-agent GDC-9545, and patients in the control group will receive single-agent endocrine therapy per physician's choice. Endocrine monotherapy will be limited to fulvestrant or an AI. The choice of endocrine treatment is at the discretion of the investigator and should be based on various clinical considerations (e.g., age, tumor burden, symptoms, toxicity considerations, as well as appropriateness for targeted therapy) and local practice.

3.3.4 Rationale for Primary Endpoint of Investigator-Assessed Progression-Free Survival

PFS is regarded as a clinically relevant measure of treatment benefit and, in recent years, has been shown to be an approvable endpoint in the setting of HR-positive, HER2-negative metastatic breast cancer for several drugs. In the PALOMA-3 study of patients with previously treated HR-positive, HER2-negative advanced or metastatic breast cancer (NCT01942135), median PFS for palbociclib plus fulvestrant versus fulvestrant were 9.5 months (95% CI: 9.2 to 11.0 months) and 4.6 months (95% CI: 3.5 to 5.6 months), respectively (hazard ratio = 0.461; 95% CI: 0.360 to 0.591; $p < 0.0001$) (Cristofanilli et al. 2016).

Data from the Phase III BOLERO-2 study (NCT00863655) of exemestane plus everolimus versus exemestane, in postmenopausal women with HR-positive advanced breast cancer that had progressed or recurred during treatment with a nonsteroidal AI, demonstrated a median PFS of 11.0 versus 4.1 months, respectively (hazard ratio = 0.38; 95% CI: 0.31 to 0.48; $p < 0.0001$) (Baselga et al. 2012; Yardley et al. 2013).

In the Phase III CONFIRM study (NCT00099437), median PFS for fulvestrant 500 mg versus fulvestrant 250 mg was 7.9 versus 6.3 months, respectively (hazard ratio=0.80; 95% CI: 0.70 to 1.10; p=0.068) for HR-positive locally advanced or metastatic breast cancer in the second-line setting (patients who relapsed more than 12 months after completion of adjuvant therapy, or who had previously presented with de novo locally advanced or metastatic breast cancer and were required to have a prior line of endocrine therapy [anti-estrogen or AI] for advanced disease) (Di Leo et al. 2010; Di Leo et al. 2018).

Based on the data from these Phase III studies, PFS has been chosen as the primary endpoint for this proposed Phase II study, which aims to demonstrate an improvement in median PFS for GDC-9545 compared with physician's choice of endocrine monotherapy.

PFS will be determined by the investigator according to RECIST v1.1; a retrospective, blinded, independent central evaluation of disease response and progression may be conducted by an IRC as outlined in Section 3.1.2.

3.3.5 Rationale for Biomarker Assessments

ER-positive, HER2-negative breast cancer is a heterogeneous disease (Koboldt et al. [The Cancer Genome Atlas Network] 2012). Therefore, all patients may not be equally likely to benefit from treatment with GDC-9545. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients who are most likely to respond to GDC-9545. PD biomarkers will be assessed to demonstrate evidence of biologic activity of GDC-9545 in patients and to inform potential revisions to the PK sample–collection schedule. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored. Biomarker data will not inform clinical decisions and patient management.

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.

3.3.5.1 Rationale for the Collection of Plasma Samples for Somatic Tumor Mutation Analysis

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

3.3.5.2 Rationale for the Collection of Tissue Samples

Archival or fresh tumor tissue (preferred) will be collected. A specimen from the most recently obtained tumor tissue will be requested to obtain the most accurate reflection of a patient's current disease, while minimizing burden. Tumor tissues may be assessed for ER, progesterone receptor, and HER2 protein levels, and proliferative index (Ki67). In addition, tumor tissue may enable assessment of ER pathway activity using RNA analysis of ER target genes (Guan et al. 2019). NGS techniques such as targeted exome sequencing may offer a unique opportunity to identify biomarkers of response and/or resistance to GDC-9545 in tumor tissue. 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. Mutations in the *ESR1* gene are more prevalent in metastatic ER-positive tumors and have been correlated with resistance to anti-estrogen therapies (Robinson et al. 2013; Toy et al. 2013; Jeselsohn et al. 2014). Tumor tissue analysis offers the opportunity to perform molecular subtyping that may inform breast cancer biology and response to GDC-9545 or endocrine therapy. The collection of tissue samples may also support future diagnostic development.

Tissue samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or whole exome sequencing (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. 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.

3.3.6 Rationale for Clinical Outcome Assessments

As metastatic breast cancer is not curable with currently approved and available therapies, the primary focus for patients is prolonging life and delaying the progression of cancer, while maintaining quality of life and the ability to carry out daily activities (Cardoso et al. 2012). Research indicates that a higher proportion of HR-positive patients have bone metastases compared with other subtypes, which is often associated with pain (Irvin et al. 2011; Wood et al. 2016); thus, disease-related pain may be an important variable to assess during treatment. Limited data are available characterizing the clinical presentation of disease in this population; however, it is hypothesized that progression of disease would be associated with an increase in pain symptoms. Hence, examining and measuring patients' disease-related pain and interference with functioning is important.

Additionally, 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 tolerability information directly from patients can provide a better understanding of treatment characteristics and their effects.

These issues will be assessed using validated PRO assessments in patients enrolled in the study. The QLQ-C30 will be administered to patients to assess disease and treatment-related symptoms, functioning, and GHS/QoL. The QLQ-BR23 will provide an additional assessment of some treatment-related symptoms and symptoms that may occur with advanced disease. The "worst pain" item from the BPI-SF will be used to gain further insight into increase in pain severity. For evaluation of the tolerability of GDC-9545, patients will be asked to report on their experience related to diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash selected from the validated PRO-CTCAE item bank. These symptoms were identified as being salient to patients' experience with GDC-9545 and/or common endocrine therapies on the basis of preliminary and published safety data, respectively. An additional exploratory safety endpoint has been specified to evaluate the overall treatment burden patients may experience, which will be assessed by analyzing the proportion of patients who select each response option at each assessment timepoint by treatment arm for the single-item GP5 ("I am bothered by side effects of treatment") from the Physical Well-Being subscale of the validated and reliable FACT-G instrument,

Version 4 (Cella et al. 1993; Webster et al. 1999). The EQ-5D-5L will also be collected and utilized to derive health states for use in economic models; therefore, the results will not be reported in the Clinical Study Report. See Section 4.5.9 and Appendix 5–Appendix 10 for additional details on PRO instruments used in this study.

The PRO data collected in the study will be supplemented by (optional) interviews conducted among a subset (up to 30) of patients treated with GDC-9545 to further understand the experiences of study treatment, therapeutic context, and disease journey from the patient perspective.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 300 patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer who have received one or two prior lines of systemic therapy in the locally advanced or metastatic setting will be enrolled during the global enrollment phase of this study. After completion of the global enrollment phase, additional patients may be enrolled in an extended China enrollment phase.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- For women: postmenopausal or premenopausal/perimenopausal status, defined as follows:

  Postmenopausal, as defined by at least one of the following criteria:

  – Age ≥ 60 years

  – Age < 60 years and ≥ 12 months of amenorrhea without an alternative medical cause plus follicle-stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment, in the absence of oral contraceptive pills, hormone replacement therapy, or gonadotropin-releasing hormone agonist or antagonist.

  – Documented bilateral oophorectomy (≥ 14 days prior to first treatment on Day 1 of Cycle 1 and recovery from surgery to baseline)

  Premenopausal or perimenopausal, defined as not meeting the criteria for postmenopausal, and willing to undergo and maintain treatment with approved LHRH-agonist therapy for the duration of study treatment

  LHRH-agonist therapy may be initiated 28 days prior to Day 1 of Cycle 1 (or according to clinical practice for the selected agent). To

minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end of the treatment cycle, monthly injections of LHRH agonist are preferred and to be synchronized with Day 1 of each 28-day cycle.

- For men: willing to undergo and maintain treatment with approved LHRH-agonist therapy for the duration of study treatment

  LHRH-agonist therapy may be initiated 28 days prior to Day 1 of Cycle 1 (or according to clinical practice for the selected agent). To minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end of the treatment cycle, monthly injections of LHRH agonist are preferred and to be synchronized with Day 1 of each 28-day cycle.

- Locally advanced or metastatic adenocarcinoma of the breast, not amenable to treatment with curative intent
- Disease progression after treatment with one or two lines of systemic therapy in the locally advanced or metastatic setting

  One of the prior lines of systemic therapy may have included chemotherapy.

  Patients may not have received more than one prior targeted therapy regimen in the locally advanced or metastatic setting. Targeted therapies may include, but are not limited to, CDK4/6 inhibitors, mTOR inhibitors, PI3K inhibitors or PARP inhibitors.

  One of the prior lines of systemic therapy must have included endocrine therapy, which must have been administered continuously for a minimum of 6 months in the locally advanced or metastatic setting prior to disease progression.

  Patients who were intolerant to their last systemic anti-cancer regimen may be considered eligible if all other eligibility criteria are met (including a minimum of 6 months continuous endocrine therapy).

  Intolerance is defined as any treatment-related Grade 4 adverse event, or any treatment-related Grade 2 or 3 adverse event that is unacceptable to the patient and persists despite standard countermeasures. The reason for intolerance must be fully documented.

- Documented ER-positive tumor according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) or ESMO guidelines, assessed locally and defined as $\geq$1% of tumor cells stained positive based on the most recent tumor biopsy (or archived tumor sample)

  Patient must be considered appropriate for endocrine therapy.

- Documented HER2-negative tumor assessed locally and defined as meeting criteria according to ASCO/CAP guidelines (Wolff et al. 2018).

- Confirmed availability of the most recently collected and representative tumor tissue specimen suitable for biomarker testing with de-identified associated pathology report is required (i.e., archived formalin-fixed, paraffin-embedded [FFPE] tissue block [preferred] or 15–20 slides containing unstained, freshly cut, serial sections). Whenever possible, tumor tissue from a metastatic site of disease is preferred, but archival tumor tissue from the primary tumor is acceptable if it is the most recently collected or most suitable for testing (see Section 4.5.7 and the laboratory manual)

  If tumor tissue is not available, a newly collected, pre-treatment biopsy will be required for patient participation. In general, a minimum of three cores per block is preferred.

  If the aforementioned minimum tissue requirements cannot be met because of local regulatory requirements, patient may still be eligible for the study and study team is available for advice.
- Measurable disease as defined per RECIST v.1.1 or bone only disease which must have at least one predominantly lytic bone lesion confirmed by CT or MRI which can be followed.

  Tumor lesions previously irradiated or subjected to other locoregional therapy will be deemed measurable only if disease progression at the treated site after completion of therapy is clearly documented.
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0–1
- Life expectancy of >6 months
- 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 $\leq 3 \times$ upper limit of normal (ULN)

    For patients with documented liver metastasis: AST and ALT $\leq 5 \times$ ULN
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    The blood counts are to meet the specified criteria without transfusion or growth factor support, unless it is clear that the bone marrow function is adequate and that any aberration has a clear and correctable cause, and the correction undertaken.
  - 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 (or PT) $< 1.5 \times$ ULN and PTT (or aPTT) $< 1.5 \times$ ULN (except for patients receiving anticoagulation therapy)

  For patients receiving 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's 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.

- Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE v5.0 Grade ≤1 (except alopecia, Grade ≤2 peripheral neuropathy, or other toxicities not considered a safety risk for the patient per investigator's judgment)
- For women of childbearing potential: agreement to take precautions as outlined below for each treatment arm
  - If assigned to the control arm (physician's choice of endocrine monotherapy), agreement to comply with local prescribing guidelines regarding contraception for the chosen endocrine monotherapy
  - If assigned to the GDC-9545 arm: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

    Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of < 1% per year during the treatment period and for *10* days after the final dose of GDC-9545 or for the time period according to local prescribing guidelines. Women must refrain from donating eggs during this same period.

    A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

    For women of childbearing potential, hormonal contraceptive methods are not allowed in this study.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. LHRH agonists are not adequate contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to take precautions as outlined below for each treatment arm:
  - If assigned to the control arm (physician's choice of endocrine monotherapy), agreement to comply with local prescribing guidelines regarding contraception for the chosen endocrine monotherapy
  - If assigned to the GDC-9545 arm: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

    With a female partner of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for 10 days after the final dose of GDC-9545 or for the time period according to local prescribing guidelines. Men must refrain from donating sperm during this same period.

    With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 10 days after the final dose of GDC-9545 or for the time period according to local prescribing guidelines to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

    The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

    For female partners of male patients, hormonal contraceptive methods supplemented by a barrier method are permitted.
- Ability to comply with the study protocol, in the investigator's judgment
- Willing and able to use an electronic device for PRO data collection

- For patients enrolled in an extended China enrollment phase: current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

4.1.2 Exclusion Criteria

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

- Prior treatment with a SERD, with the exception of fulvestrant, if fulvestrant treatment was terminated at least 28 days prior to randomization
- Treatment with any investigational therapy within 28 days prior to randomization
- Major surgery, chemotherapy, radiotherapy, or other anti-cancer therapy within 14 days prior to randomization

  Patient must have recovered from any resulting acute toxicity (to Grade 1 or better) prior to randomization.

  Anticipation of need for a major surgical procedure during the course of the study is exclusionary.
- History of any other malignancy other than breast cancer within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I endometrial cancer

  For participants with a history of other non-breast cancers within 5 years from the date of randomization and considered of very low risk of recurrence per investigator's judgment (e.g., papillary thyroid cancer treated with surgery), eligibility is to be discussed with the Sponsor.
- Advanced, symptomatic, visceral spread that is at risk of life-threatening complications in the short term (including massive uncontrolled effusions [pleural, pericardial, peritoneal] or pulmonary lymphangitis)
- Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease

  Patients with a history of CNS metastases or cord compression are eligible if have been definitively treated with local therapy (e.g., radiotherapy, surgery), are clinically stable, and have not been treated with anticonvulsants or corticosteroids within 2 weeks prior to randomization.
- Active cardiac disease or history of cardiac dysfunction, including any of the following:
  - History (within 2 years of screening) or presence of idiopathic symptomatic bradycardia or resting heart rate $<$50 bpm at screening

    Patients on stable dose of a β-blocker or calcium channel antagonist for preexisting baseline conditions (e.g., hypertension) may be eligible if resting heart rate is at least 50 bpm.

- History of angina pectoris or symptomatic congestive heart disease within 12 months prior to study entry
- History of documented congestive heart failure (New York Heart Association Class II–IV) or cardiomyopathy
- QT interval corrected through use of Fridericia's formula (QTcF) >470 ms for women, >450 ms for men, history of long or short QT syndrome, Brugada syndrome or known history of corrected QT interval prolongation, or torsades de pointes
- 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.
  - Participants with first-degree heart block may be considered for inclusion following consultation with a cardiologist and determination that no additional cardiac risks are present.
  - Patients with history of well-controlled atrial fibrillation are eligible.
- History (within 12 months) or presence of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as significant structural heart disease (e.g., severe left ventricular systolic dysfunction,) restrictive cardiomyopathy, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, moderate to severe valve disease) or family history of long QT syndrome
  - Clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia) should be corrected prior to enrollment,

- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis virus (e.g., hepatitis B or hepatitis C), current alcohol abuse, or cirrhosis

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

  Patients that have tested positive for anti-HBc would be eligible if tests for HBsAg and polymerase chain reaction (PCR) are HBV DNA are negative.

  Patients who have been cured of their HCV infection (must have an undetectable viral load i.e., a sustained virologic response for 3 months after completing treatment) are eligible to enroll. Patients that have tested positive for the HCV antibody would be eligible if tests for HCV RNA are negative. If the patient is a carrier of HCV and tests positive for HCV RNA, they would not be considered eligible.

  For patients who have been successfully treated for viral hepatitis, the possibility of re-activation of the virus or reinfection with viral hepatitis should

be considered by the Investigator and the overall potential benefits associated with study treatment for the patient should be deemed to exceed the overall risks.

- Known HIV infection
- Active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or major upper gastrointestinal (GI) surgery, including gastric resection, potentially affecting enteral absorption
- Serious infection requiring oral or IV antibiotics, or other clinically significant infection, within 14 days prior to randomization. Patients who fully recovered from serious and clinically significant infections within 14 days prior to randomization 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
- Known allergy or hypersensitivity to any of the study drugs or any of their excipients
- For premenopausal/perimenopausal patients or male patients: known hypersensitivity to LHRH agonists
- Pregnant or breastfeeding, or intending to become pregnant during the study or within *10* days after the final dose of GDC-9545, or within the time period specified per local prescribing guidelines after the final dose of physician's choice of endocrine monotherapy

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 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 to receive either GDC-9545 or physician's choice of endocrine monotherapy. 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 factors:

- Site of disease (visceral vs. non-visceral), locally assessed

  Visceral is defined as any lung and/or liver involvement.

  Non-visceral is defined as absence of any lung and/or liver involvement.

- Prior treatment with a CDK4/6 inhibitor (yes vs. no)
- Prior treatment with fulvestrant (yes vs. no)

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are GDC-9545 and physician's choice of endocrine monotherapy. LHRH agonists are considered non-IMPs.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 GDC-9545

GDC-9545 will be supplied by the Sponsor as an immediate-release capsule. Each GDC-9545 capsule contains 30 mg of GDC-9545 (free base equivalent), packaged in high-density polyethylene bottles with a plastic child-resistant cap with induction seal and desiccant. For information on the formulation of GDC-9545, see the pharmacy manual and the GDC-9545 Investigator's Brochure.

4.3.1.2 Physician's Choice of Endocrine Monotherapy

The physician's choice of endocrine monotherapy will be limited to fulvestrant or an AI and will be either provided by the Sponsor where required by local health authority regulations or sourced locally by the site with reimbursement by the Sponsor. The options are fulvestrant, letrozole, anastrozole, exemestane, formestane, aminoglutethimide, and testolactone. For information on the formulation and packaging, see the local prescribing information for the respective product.

4.3.1.3 Luteinizing Hormone–Releasing Hormone Agonist

For premenopausal/perimenopausal patients (as defined in Section 4.1.1) and male patients in both treatment arms, the investigator will determine and supply the appropriate LHRH agonist locally approved for use in breast cancer. Acceptable agents include, but are not limited to, leuprolide acetate, goserelin acetate, or triptorelin pamoate. The investigator will determine and supply the appropriate LHRH agonist locally approved for use in breast cancer. If the patient becomes intolerant to current LHRH agonist, the patient may switch to another approved LHRH agonist during the study.

To minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end of the treatment cycle, monthly injections of LHRH agonist are preferred and to be synchronized with Day 1 of each 28-day cycle.

For information on the formulation and packaging of the LHRH agonist, see the local prescribing information for the respective product.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1. Patients should receive the first dose of study drug on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 3 days after randomization.

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

Details on treatment administration (e.g., dose and timing) 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 5.3.5.12.

At the beginning of each patient's study participation, site study staff will provide the patient 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. For GDC-9545 and any other study drug administered at home, the medication diary, unused study drug, and study drug containers (used or unused) should be collected and reviewed for drug accountability at the beginning of each cycle.

Capsules (or tablets, as applicable) that are not returned will be considered to have been taken, unless otherwise specified in the patient's diary/eCRF. Note that dosing eCRFs should be completed using the following prioritization (in the event of discrepancies): 1) site pharmacy drug accountability logs (IMP disbursed minus IMP returned); 2) patient daily dosing diary; and 3) clinic visit patient interview notes.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 GDC-9545

GDC-9545 should be taken orally at approximately the same time each day. Starting with Day 1 of Cycle 1, and on Day 1 of each 28-day cycle thereafter, GDC-9545 will be administered in the clinic, as indicated in the schedule of activities (see Appendix 1). Date and time of GDC-9545 dosing in the clinic should be accurately recorded for all cycles and, in particular, on days when PK sampling is performed. All other doses will be taken at home on all non-clinic visit days. GDC-9545 may be taken with or without a meal. GDC-9545 should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a dose is missed it should be made up unless the next dose is due within 6 hours. If the patient vomits at any time after taking a dose, an additional

dose should not be taken that day. Treatment may resume the next day as prescribed.

4.3.2.2 Physician's Choice of Endocrine Monotherapy

Dose administration of physician's choice of endocrine monotherapy should be performed in accordance with the local prescribing information for the respective product.

4.3.2.3 Luteinizing Hormone–Releasing Hormone Agonist

Starting with Cycle 1, LHRH agonist will be administered by site staff to male patients and premenopausal/perimenopausal patients on Day 1 of each 28-day cycle (or according to clinical practice for the selected agent). To minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end of the treatment cycle, and to minimize the number of clinic visits, monthly injections of LHRH agonist are preferred and to be synchronized with Day 1 of each 28-day cycle. In the event of dose delay of study drug, LHRH agonists should continue to be administered monthly.

4.3.3 Investigational Medicinal Product Handling and Accountability

GDC-9545 will be provided by the Sponsor. As the choice of endocrine monotherapy is left to the physician's discretion, these IMPs will be either provided by the Sponsor where required by local health authority regulations or sourced locally by the site with reimbursement 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, either by time monitoring (shipment arrival date and time) or temperature monitoring, 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/or the local prescribing information for physician's choice of endocrine monotherapy 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

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 treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Preliminary data from the Study GP44001 showed that itraconazole, a strong CYP3A inhibitor, increased giredestrant exposure to approximately 3.98-fold. Carbamazepine, a strong CYP3A inducer, decreased giredestrant exposure by approximately 75%. The results suggest giredestrant is a moderately sensitive CYP3A substrate.

The prescribing information/labels of any concomitant medication must be reviewed and the overall benefits and risks to the patient associated with the concomitant medications judged before the concomitant medications are used.

4.4.1 Permitted Therapy

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

- Approved COVID-19 vaccines and treatments (including those with emergency use authorizations), according to prescribing information/label.
- Symptomatic anti-emetics, anti-diarrheal therapy, and other palliative and supportive care for disease-related symptoms may be administered at the investigator's discretion. All concomitant medication and/or therapies should be documented in the patient's eCRF.
- Pain medications administered per standard clinical practice are acceptable while the patient is enrolled in the study and are to be recorded on the Concomitant Medications eCRF.
- Bone-sparing agents (e.g., bisphosphonates, denosumab) for the treatment of osteoporosis/osteopenia or for palliation of bone metastases are allowed during the study. It is preferred that patients are on stable doses prior to Day 1 of Cycle 1 to reduce the possibility of bone flare.

In certain instances, focal radiation therapy for palliation of bone disease-related symptoms might be allowed after discussion with the Sponsor (see Section 4.4.3); however, the need for radiation therapy will generally be considered indicative of progressive disease.

4.4.2 Cautionary Therapy for Patients Receiving GDC-9545

The following guidelines on cautionary therapy apply only to patients receiving GDC-9545. For guidelines on cautionary therapy for patients receiving physician's choice of endocrine monotherapy (control arm), refer to the local prescribing information for the respective product.

4.4.2.1 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 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.

4.4.2.2 Surgery

Patients who require surgery as part of medical treatment in the absence of disease progression must exercise caution, and GDC-9545 should be

temporarily held for at least 7 days prior to major elective surgery. After the temporary treatment hold is complete, GDC-9545 may be re-initiated based upon a clinical assessment of satisfactory wound healing and recovery from surgery.

4.4.2.3 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions (DDIs) are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

4.4.2.4 *Moderate CYP3A Inducers*

Where possible and feasible, investigators should consider alternatives to the concomitant administration of moderate CYP3A inducers with giredestrant. If this is not possible or there are no suitable alternatives, co-administration with moderate CYP3A inducers should be generally limited to short term use (approximately 30 days).

4.4.3 Prohibited Therapy

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

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Any concomitant therapy intended for the treatment of cancer (other than protocol-mandated study treatment) including, but not limited to, chemotherapy, immunotherapy, biologic therapy, radiotherapy, or herbal therapy is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment.
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate, and selective ER modulators (e.g., raloxifene) are prohibited unless required to treat adverse events.

  For female trial participants hormonal contraceptives are prohibited. For female partners of male participants refer to Section 4.1.1.
- Radiotherapy for unequivocal progressive disease is prohibited, with the exception of new brain metastases in the setting of systemic response as follows:

  Patients who have demonstrated control of their systemic disease (defined as having received clinical benefit [i.e., a PR, CR, or SD for ≥24 weeks]), but who have developed isolated brain metastases that are treatable with radiation, will be allowed to continue to receive study treatment until systemic progression of disease and/or further progression in the brain (based on investigator assessments).

Endocrine therapy (i.e., GDC-9545 or physician's choice) may be administered concomitantly with radiotherapy. Patients should not miss more than one cycle of study treatment due to radiotherapy and must meet eligibility requirements to continue study treatment (see Section 4.1.1).

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

  Further reasons for avoiding local radiotherapy include the difficulty in distinguishing new symptomatic pain or worsening of lytic bone lesions from disease progression. TTD in pain is a secondary endpoint of this study and palliative radiotherapy may alter these results. As such, advice from Medical Monitor for palliative radiotherapy to bone in the absence of disease progression may be considered.

  Endocrine therapy (i.e., GDC-9545 or physician's choice) may be administered concomitantly with radiotherapy. Patients should not miss more than one cycle of study treatment due to radiotherapy and must meet eligibility requirements to continue study treatment (see Section 4.1.1).

  Previous clinical experience also suggests that new bone pain is frequently a symptom of disease progression. Bone pain can be treated with pain medications, nonsteroidal anti-inflammatory drugs, or corticosteroids.

- 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 Medical Monitor can be consulted.

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

Co-administration of giredestrant with the following concomitant therapies should be avoided:

- *Strong CYP3A inhibitors, including, but not limited to, the following: atazanavir, ritonavir, lopinavir, telaprevir, telithomycin, indinavir, nelfinavir, saquinavir, clarithromycin, troleandomycin, itraconazole, ketoconazole, voriconazole, posaconazole, nefazodone, mibefradil*
- *Strong CYP3A inducers, including, but not limited to, the following: apalutamide rifampin, carbamazepine, phenytoin, enzalutamide, lumacaftor, and hyperforin (St. John's Wort).*

The above lists of CYP3A concomitant medications are not necessarily comprehensive. Thus, the investigator should consult local prescribing information for any concomitant medication as well as the internet reference provided below when determining whether a certain medication strongly inhibits or induces CYP3A. If the benefit from the use of a strong CYP3A inhibitor or strong CYP3A inducer outweighs the risk and no suitable alternative is available, a strong CYP3A inhibitor or strong CYP3A inducer may be used for a short period of up to 2 weeks. Giredestrant should be withheld during the use of a strong CYP3A inhibitor (e.g., before initiating and during the 5-day COVID-19 treatment with PAXLOVID™ [containing the strong CYP3A inhibitor ritonavir]).

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

4.4.4 ***Prohibited Food***

Consumption of grapefruit, grapefruit juice, grapefruit supplements, or Seville oranges (potent CYP3A 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. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations) and may be obtained up to 6 weeks before initiation of study treatment. 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. If a patient does not meet all eligibility criteria, the patient may qualify for one re-screening opportunity 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 prior cancer therapies and procedures), and reproductive status will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. 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 postbaseline 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.

4.5.4 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.

4.5.5 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 11) and recorded on the eCRF.

4.5.6 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of physical examinations, CT scans, MRI scans, and bone scans, according to RECIST v1.1 (see Appendix 4).

CT scans should include chest, abdomen, and pelvic scans; CT scans of any other sites of disease should be included if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

The CT scans, including brain CT scan (when clinically indicated), should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease.

Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the eCRF.

Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions. Abnormalities identified on bone scans must be confirmed by X-ray, CT scan with bone windows, or MRI scan. Special considerations regarding the measurability of bone lesions are outlined in RECIST v1.1 (see Appendix 4).

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

- All lesions identified at baseline (target and non-target) will be reassessed using the same imaging method throughout the course of the study. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator to ensure internal consistency across visits.
- All CT scans and other relevant imaging such as MRIs obtained for all patients enrolled at the study site should be reviewed by the local radiologist who, together with the investigator, will determine the local assessment of response and progression. All bone scans obtained from patients with bone metastases should also be reviewed similarly.

- Images for all tumor assessments will be prospectively collected to enable a retrospective, blinded, independent central review.

Recent literature indicates that vaccination-related adenopathy (enlarged lymph nodes) on radiologic imaging (e.g., CT, MRI) and transient uptake on PET scan are frequent findings (up to 16% in vaccine trials) after administration of COVID-19 vaccines (Polack et al. 2020; CDC 2021; Grimm et al. 2021, McIntosh et al. 2021; Becker et al. 2021). These findings may appear similar to malignant nodal involvement and hence impact image interpretation.

Concerns or confusion regarding vaccine-induced lymphadenopathy should not delay COVID-19 vaccination, particularly as the mortality related to COVID-19 is higher in cancer patients than the general population.

If possible, and when it does not unduly delay care, screening tumor assessments should be performed prior to the first dose of a COVID-19 vaccination or 4–6 weeks following the second dose of a COVID-19 vaccination. On-study tumor assessment schedule should be followed as closely as possible. After COVID-19 vaccination, performing additional follow-up tumor assessments should be considered, to ensure resolution of any possible confounding findings.

4.5.6.1 Baseline Tumor Assessments

Baseline tumor assessment should be performed at screening within 28 days prior to randomization (unless otherwise specified) and will include the following assessments:

- CT or MRI scan of the chest, abdomen, and pelvis
- CT or MRI scan of brain, in patients with previously treated brain lesions

  The scan must be within the screening window and ≥4 weeks after the completion of radiotherapy. For all other patients, brain scans should be acquired if clinically indicated.
- CT or MRI scan of any other sites of disease as clinically indicated
- Clinical assessment of superficial disease, including photographs of all superficial metastatic lesions
- Bone scans or other institutional standard bone imaging

Radiographic tumor assessments and bone scans performed as routine procedures before the signing of the Informed Consent Form may be accepted as baseline assessments provided the following criteria are met:

- The tests were performed per the method requirements outlined above
- Appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes
- For bone scans: performed within 6 weeks prior to randomization

4.5.6.2 Postbaseline Tumor Assessments

Postbaseline tumor assessments will be performed according to the schedule below, from randomization, regardless of dose delay, until radiographically and/or clinically (i.e., for photographed or palpable lesions) disease progression as assessed by the investigator according to RECIST v1.1 (see Appendix 4), except in the case of isolated brain metastases as described in Section 4.4.3. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new anti-cancer therapy. For patients with symptomatic deterioration, every effort should be made to provide documented progression via radiographic modality. Tumor assessments should be scheduled relative to the date of randomization rather than the date of the previous tumor assessment.

The following postbaseline tumor assessments will be performed every 8 weeks (±7 days) from randomization for the first 18 months, then every 12 weeks (±7 days) thereafter:

- CT or MRI scan of the chest, abdomen, and pelvis
- CT or MRI scan of brain if clinically indicated
- CT or MRI scan of any other sites of disease identified at baseline
- Clinical assessment of sites of superficial disease identified at baseline
- For patients with bone lesions at baseline: X-ray, CT scan, or MRI scan of selected evaluable bone lesions, ensuring consistent use of the same modality for all evaluations

  Bone scans are required to confirm CR; however, areas that have received palliative radiotherapy during the study cannot be used to assess response to study treatment.

Postbaseline bone scans will be performed every 24 weeks (±7 days) or as clinically indicated.

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

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples should be drawn according to the schedules of activities (see Appendix 1, Appendix 2, and Appendix 3). For patients receiving GDC-9545, laboratory samples should be drawn within 72 hours prior to study drug administration and results of the following assessments should be available for review at each clinic visit prior to dosing to inform dosing decisions: complete blood count, total bilirubin, ALP, AST, ALT, creatinine, BUN, and pregnancy test.

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, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening, within 7 days prior to initiation of study treatment. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Coagulation: INR (or PT), PTT (or aPTT)
- FSH and estradiol (for premenopausal/perimenopausal patients and female patients aged $<$60 years)

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Plasma samples for PK analysis (GDC-9545 arm only)
- Plasma sample for determination of *ESR1* mutation status
  - Determination of ESR1 mutation status will be made using the FoundationOne Liquid CDx assay or an assay from an approved regional vendor.
- Blood and plasma samples for exploratory research on biomarkers and biomarker assay development
- Archival or newly collected tumor tissue sample obtained at baseline upon confirmation of enrollment onto the study for exploratory research on biomarkers

  Confirmed availability of the most recently collected and representative archived FFPE tumor tissue block (preferred) or approximately 15–20 slides (11–15 slides in China) containing unstained, freshly cut, serial sections along with an associated de-identified pathology report is required prior to study enrollment. Whenever possible, tumor tissue for a metastatic site of disease is preferred, but archival tumor tissue from the

primary tumor is acceptable if it is the most recently collected or most suitable for testing.

Tumor tissue should be of good quality based on total and viable tumor content. Samples should 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 (three cores preferred, embedded in a single paraffin block), or excisional, incisional, 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, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases is not acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a newly collected pretreatment tumor biopsy is required. A tumor biopsy of the growing lesion is preferred. 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.

Exploratory biomarker research may include, but will not be limited to, analysis of circulating tumor DNA, 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 WGS or WES of blood, plasma, and tissue samples, but WGS or WES of blood samples will be performed only at participating sites (see Section 4.5.10). Tumor tissue, plasma, and blood samples may be used for future research and/or development of disease-related tests or tools.

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

- Plasma samples collected for PK analysis may be needed for drug metabolism research; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

- Blood, plasma, and tumor tissue samples collected for biomarker research 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
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the date of final closure of the clinical database, whichever occurs first.

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 (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.

4.5.8 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. 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 medical 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. Digital recordings will be stored at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the

machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another 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 5.1.3.4. 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).

4.5.9 Clinical Outcome Assessments

PRO data will be collected to more fully characterize the clinical profile of GDC-9545 in patients enrolled in the study. PRO data will be collected via electronic questionnaires at the clinic sites using the following instruments: QLQ-C30, QLQ-BR23, "worst pain" item from the BPI-SF, select items of the PRO-CTCAE, the FACT-G single-item GP5 for overall treatment burden, and the EQ-5D-5L. The questionnaires, translated into the local language as appropriate, will be distributed by the site staff and completed in their entirety by the patient at baseline (Day 1 of Cycle 1) and as noted in the schedule of activities (see Appendix 1).

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at the clinic at the timepoints specified in the schedule of activities (see Appendix 1):

At the clinic, instruments will be 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, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. In case the PRO device is not available at site or not functioning, a web-based or paper backup process may be

used instead. Under this process, web-based or printed questionnaires will be self-administered (i.e., completed by patients themselves in the same order and with the same content [including language versions] as when the device is used). Site staff should review the completed questionnaires to ask patients to rectify unclear responses and/or to confirm if an item is intentionally left blank. Site staff will enter PRO data collected via paper into the same centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

If a PRO questionnaire is not available in a patient's native language, the patient will be exempt from completing that specific assessment.

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 10−15 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.

4.5.9.2 Description of Clinical Outcome Assessment Instruments

EORTC QLQ C30

The QLQ-C30 (see Appendix 5) is a validated and reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health and quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The QLQ-C30 module takes approximately 10 minutes to complete.

EORTC QLQ-BR23

The QLQ-BR23 breast cancer module (see Appendix 6) is meant for use among patients diagnosed with breast cancer (Sprangers et al. 1996). The breast cancer module incorporates five multiple-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image, and sexual functioning. In addition, single items assess sexual enjoyment, hair loss, and future perspective. Male patients may be exempt from some of the questions included in the QLQ-BR23 breast cancer module.

BPI-SF "Worst Pain" Item

Cancer-related pain severity will be assessed using the BPI-SF "worst pain" item (see Appendix 7), a patient-reported measure rated on a 10-point numeric rating scale, with 0 meaning "no pain" and 10 indicating "worst pain you can imagine." This assessment approach follows consensus recommendations for measuring pain in clinical trials and is commonly used as a standalone item across diseases (including breast cancer), therapies, and languages (Dworkin et al. 2005; Harrington et al. 2014). Patients will complete the pain severity assessment at each monthly visit using a 24-hour recall assessment window. A threshold of $\geq$2 points, used to indicate clinically meaningful deterioration on the pain severity numeric rating scale, has been well-documented in patients with breast cancer and will be applied in this study (Cleeland et al. 2009; Mathias et al. 2010).

EQ-5D-5L

The EQ-5D-5L (see Appendix 9), is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic modeling and will be included only descriptively in the Clinical Study Report.

PRO-CTCAE

The PRO-CTCAE (see Appendix 8) 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.

The PRO-CTCAE item bank was designed and validated as a repository of standalone items. A subset of seven symptoms deemed most applicable to the current treatments has been selected for this study, i.e., diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash. 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 based on preliminary safety or published studies.

FACT-G Single-Item GP5

The FACT-G instrument, Version 4 (see Appendix 10), is a validated and reliable 27-item questionnaire comprised of 4 subscales that measure physical (7 items), social and family (7 items), emotional (6 items), and functional well-being (7 items), and is considered appropriate for use with patients with any form of cancer (Cella et al. 1993; Webster et al. 1999). In this study, the single-item GP5 ("I am bothered by side effects of treatment") from the Physical Well-Being subscale of the FACT-G has been selected for individual item analysis to document the level of bother of symptoms on patient's lives. Patients will assess how true the statement "I am bothered by side effects of treatment" has been for them in the previous 7 days on a 5-point scale (0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; 4, very much). The single-item GP5 from the FACT-G takes less than 1 minute to complete.

4.5.9.3 Optional Patient Interviews

Patient interviews will be conducted among a subset of study participants (up to 30 patients in GDC-9545 arm) following Cycle 2 (this can potentially include the post-treatment period). The semi-structured interviews will be moderated by an external vendor and conducted by telephone (lasting up to an hour in duration). The interviews will explore participants' experience of study treatment, therapeutic context, and disease journey. Recording from the interviews will be transcribed and de-identified to maintain confidentiality. Additional consent for this optional study component will be included in the relevant Informed Consent Form.

4.5.10 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. WES and WGS are not applicable in China.

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. 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 4.5.10) will not be applicable at that site.

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 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 4.5.7 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Tumor Biopsy (Patients at Participating Sites)

At participating sites, consenting patients will undergo an optional tumor biopsy at time of disease progression (see Appendix 3). Tumor biopsies of the growing lesion are preferred. Patients may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. Optional tumor biopsy at time of disease progression is not applicable in China.

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 4.5.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.7 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

Tumor specimen 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.

NGS may be performed by Foundation Medicine or an alternative, approved central laboratory for that region on tumor biopsies collected at time of disease progression. If performed by Foundation Medicine, the investigator may obtain an NGS report through Foundation Medicine's web portal for results from testing performed on tissue submitted at the time of disease progression. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results will not be available for samples that do not meet criteria for testing.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 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. RBR is not applicable in China.

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

4.5.12.2 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 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

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

- Leftover blood, plasma, and tumor 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)

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).

4.5.12.4 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.

4.5.12.5 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.

4.5.12.6 Withdrawal from the Research Biosample Repository

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

global.rcr-withdrawal@roche.com

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

4.5.12.7 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 in light of the potential for treatment benefit and the severity of the event
- Disease progression per investigator assessment according to RECIST 1.1, with the exception of isolated brain metastases (see Section 4.4.3)
- Symptomatic deterioration attributed to disease progression, as assessed by the investigator
- 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 who discontinue study treatment will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit 30 (+3) days after the final dose of study treatment (unless final dose resulted in a dose delay prior to decision to discontinue). For the control arm, the upper limit of the visit window will be dependent upon maximum dosing delay as permitted per local guidelines. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit if it falls within 28 (+3) days after the patient's final dose of study treatment. After treatment discontinuation, adverse events will continue to be recorded as outlined in the schedule of activities (see Appendix 1).

Patients who discontinue study treatment for any reason other than unequivocal disease progression or death will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation (regardless of the reason), information on survival follow-up and new anti-cancer therapy will be collected via telephone calls,

patient medical records, and/or clinic visits approximately every 6 months or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study).

Refer to the schedule of activities (see Appendix 1) for details on follow-up assessments to be performed for patients who discontinue study treatment. Patients who are unwilling to return to the clinic after treatment discontinuation will no longer undergo adverse event and tumor response assessments at clinic visits but can undergo follow-up for adverse events, survival, and new anti-cancer therapy via telephone calls.

4.6.2 Patient Discontinuation from the Study

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

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

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- 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, and must also be documented in the eCRF. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

GDC-9545 is not currently approved for any indication, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with GDC-9545 in ongoing studies. The known (identified) and potential safety risks for GDC-9545 are outlined below.

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, with severity graded according to NCI CTCAE v5.0. An IMC will review safety data regularly throughout the study (see Section 3.1.3). Furthermore, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Identified Risks of GDC-9545

The identified risks are based on the data contained in GDC-9545 Investigator Brochure Version 5.

5.1.1.1 Arthralgia

Arthralgia was very common (>10%) in patients treated with GDC-9545. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Management of arthralgia should be according to local standard of care and institutional guidelines.

5.1.1.2 *Bradycardia*

Bradycardia was commonly reported in patients treated with giredestrant. All cases were non-serious and mild to moderate, with most cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Please refer to Table 1 for management guidelines.

5.1.1.3 Diarrhea

Diarrhea was very common (>10%) in patients treated with GDC-9545. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Please refer to Table 1 for management guidelines.

5.1.1.4 Dizziness

Dizziness was common (>10%) in patients treated with GDC-9545. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Dizziness should be managed according to institutional guidelines.

5.1.1.5 *Headache*

Headache was commonly reported in patients treated with giredestrant. Cases were non-serious and Grade 1 or Grade 2 in severity. Most headache events resolved without treatment.

5.1.1.6 *Hepatotoxicity*

Events of aspartate aminotransferase (AST) increased and/or alanine aminotransferase increased (ALT), were very commonly reported in patients treated with giredestrant. Events of blood bilirubin increased were commonly reported. The majority of events were Grade 1 or Grade 2, with few Grade 3 events. Overall, most events were non-serious and managed with either drug interruption or discontinuation of giredestrant, with treatment, or without any intervention. Please refer to Table 1 for management guidelines.

5.1.1.7 Hot flush

Hot flush was common (>1% to <10%) in patients treated with GDC-9545. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. Hot flush should be managed according to institutional guidelines.

5.1.1.8 Fatigue

Fatigue was very common (>10%) in patients treated with GDC-9545. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Fatigue should be managed according to institutional guidelines.

5.1.1.9 Musculoskeletal pain

Musculoskeletal pain was very common (>10%) in patients treated with GDC-9545. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Management of musculoskeletal pain should be according to institutional guidelines.

5.1.1.10 Nausea

Nausea was very common (>10%) in patients treated with GDC-9545. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Please refer to Table 1 for management guidelines.

5.1.1.11 Vomiting

Vomiting was common (>1% to <10%) in patients treated with GDC-9545. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Please refer to Table 1 for management guidelines.

5.1.2 Potential Risks Associated with GDC-9545

The potential risks associated with GDC-9545 are based on data from the GDC-9545 Investigator's Brochure Version 5. Please refer to the GDC-9545 Investigator's Brochure for further details.

Guidelines for management of patients who develop signs of the potential risks described below are provided in Section 5.1.3.

5.1.2.1 Venous Thromboembolic Events (Including Pulmonary Embolism)

No thromboembolic events related to GDC-9545 have been reported.

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.

In Study GO39932, as of the CCOD, in the single-agent cohorts at doses ranging from 10–250 mg (N=111), Grade 3 pulmonary embolism was reported in 1 patient (1.8%) treated at 100 mg and was considered unrelated to GDC-9545 by the investigator. There were no cases of VTEs reported in the 30 mg single-agent cohort.

5.1.2.2 Renal Toxicity or Increased Creatinine

In Study GO39932, no cases of acute kidney injury or adverse events of creatinine increase have been reported with single-agent GDC-9545 in doses up

to 250 mg (N=111). The following potentially relevant adverse events were reported: proteinuria and glomerular filtration rate decreased (1 patient each, 0.9%).

No trends of increase in serum creatinine levels were seen in laboratory results to date.

5.1.2.3 Changes in Female Reproductive Organs and Menopausal Symptoms

Based on the anti-estrogenic pharmacologic 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.

The following adverse events classified as “reproductive system and breast disorders” have been reported in patients in Study GO39932 who received single-agent GDC-9545 at doses of 10 to 250 mg (N=111): vulvovaginal dryness, vaginal discharge, breast pain, and vulvovaginal pruritus (all 1 patient each, with the exception of vaginal discharge which occurred in 2 patients [1.8%]); all were Grade 1.

5.1.2.4 Female and Male Fertility

In nonclinical studies, perturbation and arrest of the estrus cycle was observed microscopically in early development. There was evidence of a return to estrus cycling following a 16-week recovery period. While this finding remains incompletely explained, any patients with concerns for future fertility should be made aware of this potential issue prior to joining this study. Their concerns, including fertility preservation, should be discussed prior to enrolling in any study with GDC-9545.

No microscopic effects on male reproductive organs were attributed to administration of GDC-9545 in a 13-week study in male rats.

The effects of GDC-9545 on fertility in humans have not been studied.

5.1.2.5 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.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Dose Modifications

There is no dose modification permitted for GDC-9545 and GDC-9545 should be administered on each day during the 28-day cycle. See Section 5.1.3.3 for further details on management of adverse events associated with GDC-9545.

5.1.3.2 Treatment Interruption

GDC-9545 may be temporarily suspended or delayed for up to 28 days in patients who experience toxicity considered to be related to study drug. In the event that GDC-9545 cannot be resumed after being withheld for 28 days, the patient should be discontinued from GDC-9545 as per Section 4.6.1.

5.1.3.3 Management Guidelines

Guidelines for management of specific adverse events associated with GDC-9545 are outlined in Table 1 . Additional guidelines are provided in the subsections below.

Table 1 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., liver metastases, concomitant medications, or biliary obstruction). • Treat patient according to local standard of care. • Initiate close monitoring of LFTs until any abnormalities resolve or are assessed as stable.
Grade 3	• Withhold GDC-9545. • Consider consultation with hepatologist. If event resolves to Grade $\leq$1 within 28 days, resume GDC-9545 at full dose, continuing close monitoring of LFTs until any abnormalities resolve or are assessed as stable. • If event does not resolve to Grade $\leq$1 within 28 days, permanently discontinue GDC-9545.
Grade 4 or meets criteria as defined by Hy's Law (see Section 5.3.5.7)	• Permanently discontinue GDC-9545. • Consult with hepatologist.

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 1	• Continue GDC-9545.
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 or better.
Grade ≥ 3	• Withhold GDC-9545 until event resolves to Grade 1 or better. • Manage and treat patient according to local standard of care. • Consider consulting with gastroenterologist. • Resume GDC-9545 at regular dose once the event resolves to Grade 1 or better. • If event is recurring and patient cannot tolerate treatment, permanently discontinue GDC-9545.

GI = gastrointestinal; LFT = liver function test; ULN = upper limit of normal.

Table 1 Guidelines for Management of Patients Who Experience Adverse Events Associated with GDC-9545 (cont.)

Event	Action to Be Taken
Venous Thromboembolic Events (Including Pulmonary Embolism)	
General guidance	• Advise patients 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 1	• Continue GDC-9545.
Grade ≥2	• Withhold GDC-9545 until patient is stable (any thrombolytic therapy and in-patient anticoagulation has been completed). • 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 (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 or better and 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.
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 or better, and then resume GDC-9545 at full dose.
Grade 4	• Permanently discontinue GDC-9545.

DVT = deep vein thrombosis; PE = pulmonary embolism.

5.1.3.4 Management of Increases in QT Interval

GDC-9545 should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

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

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered

a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and Section 5.3.5.10 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 5.3.5.11)
- 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 5.3.5.7)
- 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 acute kidney injury, creatinine increase, or renal toxicity
- Grade ≥2 bradycardia
- Grade ≥2 thromboembolism

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 30 days after the final dose of study drug.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

Note: Based on the most recent version of NCI CTCAE (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 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

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

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Injection Reactions (for Patients Receiving Fulvestrant or Formestane)

Adverse events that occur during or within 24 hours after study drug administration for injectable anti-cancer therapy and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." If the adverse event is serious, associated signs and symptoms should be recorded on the dedicated "Additional case details and event narrative" section within the Adverse Event eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF.

5.3.5.2 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.

5.3.5.3 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.

5.3.5.4 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. 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.

5.3.5.5 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 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) 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).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of underlying breast cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, 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). An IMC will monitor the frequency of deaths from all causes.

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").

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

5.3.5.9 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").

5.3.5.10 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST. 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.

5.3.5.11 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

5.3.5.12 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, including omission of dosing by patient in error

  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 or qualifies as an adverse event of special interest, 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., patient forgot to take drug, 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.

5.3.5.13 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.

5.3.5.14 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

The Medical Monitor is available to the Principal Investigator to advise and answer any questions related to study inclusion or exclusion criteria and may share risk information pertinent to the patient. The Medical Monitor must refrain from providing clinical advice. The decision to enroll the patient in the study is the responsibility of the investigator. All eligibility decisions are made by the investigator and the Medical Monitor is available to advise as needed.

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details are provided separately.

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 Adverse Event/Special Situations 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 30 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper *Clinical Trial Adverse Event/Special Situations 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 >30 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant while on the study, within *10* days after the final dose of GDC-9545, or within the time period specified per local prescribing guidelines after the final dose of physician's choice of endocrine monotherapy. *The investigator should report the pregnancy on the* paper Clinical Trial Pregnancy Reporting Form *and submit it* 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 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator about the estimated date of conception if their partner becomes pregnant during the study, within 10 days after the final dose of GDC-9545, or within the time period specified per local prescribing guidelines after the final dose of physician's choice of endocrine monotherapy. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form, which 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 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.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male 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 and adverse events of special interest 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 30 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper *Clinical Trial Adverse Event/Special Situations 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 document listed below:

Drug	Document
GDC-9545	GDC-9545 Investigator's Brochure
Physician's choice of endocrine monotherapy:	
Fulvestrant	E.U. SmPC
Letrozole	E.U. SmPC
Anastrozole	E.U. SmPC
Exemestane	E.U. SmPC
Testolactone	USPI
Aminoglutethimide	USPI
Formestane	Chinese Package Insert

SmPC = Summary of Product Characteristics; USPI = U.S. Package Insert.

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary efficacy objective for this study is to evaluate the efficacy of GDC-9545 compared with physician's choice of endocrine monotherapy in patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer. Statistical analyses will be performed using two analysis populations as described below:

- Intent-to-treat (ITT) population: The ITT population will consist of all patients assigned to treatment groups as randomized by the IxRS. All efficacy analyses will be performed using the ITT population, unless otherwise specified.
- Safety-evaluable population: The safety population will consist of all patients who receive at least one dose of study drug (GDC-9545 or physician's choice of endocrine monotherapy) and will be analyzed based on the treatment received. Thus, all patients who received at least one dose of GDC-9545 are included in the GDC-9545 safety-evaluable group and all patients who received at least one dose of endocrine monotherapy per physician's choice are included in the control group. All safety analyses will be performed using the safety-evaluable population.

The global population will include all patients enrolled during the global enrollment phase (including patients enrolled in mainland China, Hong Kong, and/or Taiwan during that phase), and the China subpopulation will include all patients enrolled in mainland China, Hong Kong, and/or Taiwan (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subpopulation; the analyses described in Sections 6.1–6.8 apply to the global population, see Section 6.9 for information on the China subpopulation analyses.

The primary efficacy analysis of PFS and the details and timing of the primary efficacy analysis are outlined in Sections 6.1 and 6.4.

Details of analyses will be provided in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 300 patients will be enrolled and randomized in a 1:1 ratio to receive either GDC-9545 (experimental arm) or physician's choice of endocrine monotherapy (control arm). The sample size is determined by the primary endpoint, investigator-assessed PFS, comparing the two treatment arms.

The primary analysis of PFS will be conducted when approximately 166 PFS events from both arms are observed. The 166 PFS events allow for 80% power to detect an improvement in median PFS from 5.5 months to approximately 8.5 months (hazard ratio = 0.647) at the 5% (two-sided) level of significance. The

largest hazard ratio determined to be statistically significant at the 5% level will be approximately 0.738 (with median improvement in PFS from 5.5 to 7.5 months).

The enrollment duration is projected to be approximately 15 months after randomization of the first patient. For both the GDC-9545 and control arms, an annual loss to follow-up rate of 10% is assumed. On that basis, it is projected that the primary PFS analysis will occur approximately 18 months after the first patient is enrolled.

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 by treatment arm. Major protocol deviations, including major deviations with regard to inclusion and exclusion criteria, will also be listed and summarized by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

The evaluation of treatment group comparability between the treatment arms will include summaries of demographic and baseline characteristics, including stratification factors and patient treatment history.

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

6.4 EFFICACY ANALYSES

Unless otherwise specified, the ITT population consisting of all randomized patients, with patients grouped according to their assigned treatment, will be used for efficacy analysis.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is investigator-assessed PFS as defined in Section 2.1.1. Data for patients without the occurrence of disease progression or death as of the CCOD will be censored at the time of the last tumor assessment prior to the CCOD (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit). PFS will be compared between treatment arms using the stratified log-rank test. The hazard ratio will be estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio will be provided. The stratification factors used will be the same as the randomization stratification factors (see Section 4.2.1). Results from an unstratified analysis will also be provided. For each treatment arm, Kaplan-Meier methodology will be used to estimate the median PFS, and

the Brookmeyer-Crowley method will be used to construct the 95% CI for the median PFS. Kaplan-Meier curves will also be produced.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study, OS, ORR, DOR, and PFS (in subgroups characterized by baseline *ESR1* mutation status); and the PROs TTD in pain severity, PF, RF, GHS/QoL, and pain presence/interference and burden, are defined in Section 2.1.2. ORR and DOR are determined by the investigator according to RECIST v1.1.

6.4.2.1 Overall Survival

Data for patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of randomization plus 1 day.

The OS analyses will be conducted at the time of the primary analysis of PFS, at least 12 months after the primary analysis, and at the end of the study, which is expected to occur at least 25 months after the last patient is enrolled in the global study. OS will be hierarchically tested if the primary endpoint, PFS, is statistically significant at the primary PFS analysis. Analysis methodology for OS is the same as outlined for the primary endpoint, PFS.

6.4.2.2 Objective Response Rate

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 postbaseline tumor assessment, will be considered 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 the analysis of the primary endpoint. 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.

6.4.2.3 Duration of Response

Analysis of DOR will include only patients who had an objective response. Data for patients who have not progressed and who have not died at the time of analysis will be censored at date of the last tumor assessment.

The Kaplan-Meier approach will be used to estimate the median DOR and the corresponding 95% CIs.

6.4.2.4 Clinical Benefit Rate

CBR, defined as the proportion of patients with stable disease for ≥24 weeks or a CR or PR, as determined by the investigator according to RECIST v1.1. CBR will be analyzed using the same methods as those used for ORR.

6.4.2.5 PFS by *ESR1* Mutation Status

Investigator-assessed PFS will be analyzed in subgroups categorized by *ESR1* mutation status determined at baseline from plasma ctDNA.

Similar to PFS analysis, data for patients without the occurrence of disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit). PFS by ESR1 positive- and negative- mutation status will be compared between treatment arms using the stratified log-rank test. Hazard ratio estimates, confidence intervals and plots will follow the same methods as those used for primary endpoint PFS analysis.

6.4.2.6 Patient-Reported Outcomes

The PRO-evaluable population consists of randomized patients with at least one postbaseline assessment. Data for patients who do not have an observed deterioration at the time of the CCOD will be censored at the last non-missing assessment date. Data for patients without a postbaseline assessment will be censored at the time of randomization plus 1 day.

To evaluate TTD in pain severity, the "worst pain" item from the BPI-SF will be assessed. A 2-point change in the worst pain rating is defined as clinically meaningful (Mathias et al. 2010).

TTD in EORTC QLQ-C30 scale scores for pain presence and interference (Items 9 and 19), PF (Items 1–5), RF (Items 6 and 7), and GHS/ QoL (Items 29 and 30) will be assessed. A ≥10-point change in EORTC QLQ-C30 scale scores is defined as clinically meaningful (Osoba et al. 1998).

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for this study will be additional PROs as defined in Section 2.1.3.

Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of linear transformed scores will be reported for the "worst pain" item of the BPI-SF, as well as all scales (symptoms, functional domains, and GHS/QoL) of the QLQ-C30 and QLQ-BR23 questionnaires for each assessment timepoint. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be analyzed for each treatment arm. Line charts depicting the mean and mean changes from the baseline assessment (and 95% CIs) of items and scales over time will be provided for each treatment arm. In the event of incomplete data for all questionnaire scales, if more than 50% of the constituent items are completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For scales with less than 50% of the items completed, the scale will be considered as missing in accordance with the EORTC scoring manual guidelines (Fayers 2001).

PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm for each measure in ITT population. The compliance rate will be based on the total number of patients expected to complete the questionnaire at a particular timepoint.

Note that data collected via patient interviews will be analyzed separately, on a qualitative/descriptive basis, and will not be included in the main study database or detailed in the SAP.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of study drug (GDC-9545 or physician's choice of endocrine monotherapy), 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, serious adverse events, and adverse events of special interest will be summarized by treatment arm. All deaths will be summarized. 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 mapped to MedDRA thesaurus 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.

Selected laboratory and vital sign data will be summarized by treatment received, and grade compared with baseline and measurements outside of the normal range will be identified.

6.5.2 Exploratory Safety Analyses of PRO-CTCAE and GP5 Data

PRO-CTCAE analyses will be descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities over the course of the study. The number and percentage of patients reporting 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 postbaseline 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 *GP5* overall treatment burden item. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data.

A descriptive analysis of absolute scores and the proportion of patients selecting each response option at each assessment timepoint by treatment arm will be reported for the FACT-G single-item GP5.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients who received GDC-9545 and have at least one evaluable GDC-9545 concentration. PK parameters (e.g., area under the concentration–time curve, time to maximum concentration, maximum concentration observed, and half-life if appropriate) will be estimated from an intensive PK sample–subset patient population. Summary statistics (e.g., geometric mean, standard deviation, coefficient of variation, median, minimum, and maximum) will be presented for PK data. Plasma GDC-9545 concentration versus time data will be tabulated and plotted.

GDC-9545 PK data may be pooled and analyzed using a population PK analysis approach 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 may be presented in a separate report.

6.8 HEALTH STATUS UTILITY ANALYSES

Change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints.

6.9 CHINA SUBPOPULATION ANALYSES

The China subpopulation will include all patients enrolled in mainland China, Hong Kong, and/or Taiwan (i.e., during both the global enrollment phase and the extended China enrollment phase). Results from these analyses will be summarized in a separate Clinical Study Report.

After global recruitment is closed, additional patients in China may subsequently be enrolled, following the same randomization procedures and 1:1 ratio. The total number of patients in the China subpopulation should allow for sufficient demonstration of treatment benefit consistency between the global population and China subpopulation.

The efficacy objective of the China subpopulation analyses is to evaluate whether the efficacy of GDC-9545 compared with physician's choice of endocrine monotherapy in the China subpopulation (enrolled during both the global enrollment phase and the extended China enrollment phase) is consistent with the efficacy observed in the global population enrolled during the global enrollment phase. Therefore, no formal hypothesis testing will be performed for China subpopulation.

The China subpopulation analyses will be conducted when sufficient PFS events have occurred to demonstrate an acceptable probability of maintaining $\geq$50% of risk reduction compared with that estimated from the global population. The exact timing of analyses will be specified in the SAP.

The analysis methods for China subpopulation will be the same as for the global population unless elsewhere noted. The results of the China subpopulation analyses will be summarized in a separate report from the Clinical Study Report for the global population.

GDC-9545 concentration–time plots, concentration summaries, and PK parameters may be separately summarized for the intensively sampled patients from mainland China and the intensively sampled patients from the global population (not including mainland China). All sparse PK samples as well as the intensive PK samples will be included in a population PK analysis, where race

may be tested as a covariate on PK parameters, if appropriate. These analyses will be reported separately from the Clinical Study Report.

Further details will be provided in the SAP.

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.

PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details). In case the PRO device is not available at site or not functioning, a web-based or paper backup process may be used instead.

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 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor. In case the PRO device is not available at site or not functioning, a web-based or paper backup process may be used instead. Data collected in the printed version of the instrument will be transcribed by site staff into the same centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

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

7.4 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 7.6.

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.

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, 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 (where allowed by local regulations) 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 (where allowed by local regulations) 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 (where allowed by local regulations). 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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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. 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. 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 will provide clinical operations management, data management, and medical monitoring.

Approximately 125 sites globally will participate to enroll approximately 300 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study. An IRC will conduct a retrospective independent evaluation of disease response and progression (see Sections 3.1.2 and 3.1.3).

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/*or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation* will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

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).

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Appendix 1 Schedule of Activities

	Screening [a]		Treatment Cycles (28-day cycles)		Treatment Discontinuation Visit [b]	PRO Follow-Up	Follow-Up
			Cycles 1–2	Cycles 3 and Beyond			
Day (Window)	–28 to –1	–7 to –1	1[c] (±3 days)	1 (±3 days)	30 Days after Final Dose (+3 days)	90 Days after TD (±7 days)	Every 6 months (±7 days) [d]
Informed consent	x [e]						
Demographic data	x						
Medical history and baseline conditions	x						
Vital signs [f]	x		x	x	x		
Weight	x		x	x	x		
Height	x						
Complete physical examination [g]	x						
Limited physical examination [h]			x	x	x		
12-lead ECG [i]	x		x	Day 1 of Cycle 4, then every four cycles thereafter	x		
LVEF [j]	x						
ECOG Performance Status	x		x	x	x		
Hematology [k]		x	x	x	x		
Chemistry [l]		x	x	x	x		

Appendix 1 Schedule of Activities (cont.)

	Screening [a]		Treatment Cycles (28-day cycles)		Treatment Discontinuation Visit [b]	PRO Follow-Up	Follow-Up
			Cycles 1–2	Cycles 3 and Beyond			
Day (Window)	–28 to –1	–7 to –1	1[c] (±3 days)	1 (±3 days)	30 Days after Final Dose (+3 days)	90 Days after TD (±7 days)	Every 6 months (±7 days) [d]
Coagulation (INR [or PT], PTT [or aPTT])		x					
FSH and estradiol (for premenopausal/perimenopausal patients, and female patients aged <60 years only) [m]		x	Day 1 of each cycle for three cycles and then every three cycles thereafter, if receiving LHRH agonist				
Pregnancy test [n]		x	x [n]	x	x		
Urinalysis [o]	x		Perform as clinically indicated				
Confirmation of availability of tumor tissue specimen	x						
GDC-9545 administration QD Days 1–28 of each cycle			Administered at clinic visits (Day 1 of each cycle); otherwise administered at home [p]				
Physician's choice of endocrine monotherapy administration			Administered as per local prescribing guidelines [p]				
LHRH agonist administration [q] (for premenopausal/perimenopausal patients and male patients only)			Preferred option administered at clinic visit on Day 1 of each cycle (or according to clinical practice)				

Appendix 1 Schedule of Activities (cont.)

	Screening [a]		Treatment Cycles (28-day cycles)		Treatment Discontinuation Visit [b]	PRO Follow-Up	Follow-Up
			Cycles 1–2	Cycles 3 and Beyond			
Day (Window)	–28 to –1	–7 to –1	1[c] (±3 days)	1 (±3 days)	30 Days after Final Dose (+3 days)	90 Days after TD (±7 days)	Every 6 months (±7 days)[d]
Medication diary [r]			Complete when medication is taken at home or at clinic visit				
Tumor assessment: CT, MRI, clinical [s]	x		Every 8 weeks (±7 days) from randomization for the first 18 months, then every 12 weeks (±7 days) thereafter until PD				
Bone scan [t]	x		Every 24 weeks (±7 days) from randomization until PD				
PK samples			See Appendix 2				
Biomarker samples	See Appendix 3						
PRO-CTCAE, GP5, EORTC QLQ-C30, QLQ-BR23, BPI-SF "worst pain" item, EQ-5D-5L [u]			x	Cycle 3 and every other cycle thereafter [u]	x	x [v]	
Patient interviews (optional)[w]				Once following Cycle 2			
Concomitant medications [x]		x [x]	x	x	x		
Adverse events [y, z]	x	x	x	x	x		
Survival and new anti-cancer therapy follow-up							x [z, aa]

BPI-SF = Brief Pain Inventory–Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy–General; FSH = follicle-stimulating hormone; GP5 = General Population, Question 5; LHRH = luteinizing hormone-releasing hormone; LVEF = left ventricular ejection fraction; PD= progressive disease; PK = pharmacokinetic; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; QD = once a day; RECIST = Response Evaluation Criteria in Solid Tumors; TD = treatment discontinuation.

Notes: On treatment days that coincide with clinic visits, all assessments should be performed prior to dosing, unless otherwise specified. For patients receiving GDC-9545, laboratory samples should be drawn within 72 hours prior to study drug administration.

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

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit 30 (+3) days after their final dose of study treatment (unless final dose resulted in a dose delay prior to decision to discontinue). For the control arm, the upper limit of the visit window will be dependent upon maximum dosing delay as permitted per local guidelines. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit if it falls within 28 (+3) days after the patient's final dose of study treatment.

[c] Patients should receive their first dose of study treatment on the day of randomization, if possible, but no later than 3 business days after randomization.

[d] Patients who experience disease progression will discontinue treatment (except in the case of isolated brain metastases as outlined in Section 4.4.3) and enter a follow-up period during which survival and new anti-cancer therapy information will be collected every 6 months or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study).

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained up to 6 weeks before initiation of study treatment. Patients who do not meet the criteria for participation in this study (screen failure) must re-sign the consent form prior to re-screening.

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

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

[h] Perform a limited, symptom-directed examination at specified postbaseline timepoints and as clinically indicated at other timepoints.

[i] 12-lead ECG recordings will be obtained during screening; on Day 1 of Cycles 1, 2, and 4; on Day 1 of every four cycles thereafter (i.e., Cycles 8, 12, 16, etc.); at the treatment discontinuation visit; and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording (see Section 4.5.8).

[j] LVEF to be measured using multiple-gated acquisition scan or echocardiogram.

[k] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Complete blood count should be available for review prior to dosing to inform dosing decisions (see Section 4.5.7).

[l] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH. BUN, creatinine, total bilirubin, ALP, ALT, and AST counts should be available for review prior to dosing to inform dosing decisions (see Section 4.5.7).

[m] FSH and estradiol should be tested on Day 1 of Cycles 1–3 and on Day 1 of every three cycles thereafter, for the duration of study treatment.

[n] All women of childbearing potential will have a serum pregnancy test at screening, within 7 days prior to initiation of study treatment. Urine pregnancy tests will be performed at specified subsequent visits, starting on Day 1 of Cycle 2. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Pregnancy test should be available for review prior to dosing to inform dosing decisions (see Section 4.5.7).

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

[p] If the next cycle's Day 1 visit occurs with delay, patients should continue taking the medication at home until they use all medication dispensed.

[q] LHRH-agonist administration for premenopausal/perimenopausal patients and male patients only. To minimize the potential of exposure to the medication decreasing to sub-therapeutic levels towards the end of the treatment cycle, monthly injections of LHRH agonist are preferred and to be synchronized with Day 1 of each 28-day cycle *(*or according to clinical practice for the selected agent).

[r] Patients will receive and should be instructed to complete a medication diary. The medication diary, unused study drug, and study drug containers (used or unused) should be collected and reviewed on Day 1 of each cycle for drug accountability (see Section 4.3.2).

[s] Tumor assessments should be performed as per instructions in Section 4.5.6. All screening tumor assessments (unless otherwise specified) should be completed within 28 days prior to randomization. Brain CT/MRI is required at screening only if clinical indicated or when a patient had previously treated brain lesions. At subsequent tumor assessment time points, brain scans should be acquired if disease was present at baseline or if clinically indicated. Response must be assessed by the investigator according to RECIST v1.1 (see Appendix 4). Patients who discontinue study treatment for any reason other than disease progression or death should continue to undergo tumor assessments every 8 weeks (± 7 days) from randomization for the first 18 months, then every 12 weeks (±7 days) thereafter, as per instructions.

[t] Bone scan to be performed at screening. Evaluable bone lesions should be assessed as per RECIST v1.1 (see Appendix 4) every 8 weeks (±7 days) from randomization for the first 18 months, then every 12 weeks (±7 days) thereafter. Bone scans are to be repeated every 24 weeks (±7 days) or as clinically indicated, as per instructions in Section 4.5.6.

[u] PRO assessments (PRO-CTCAE [Appendix 8], GP5 [Appendix 10], EORTC QLQ-C30 [Appendix 5], BPI-SF "worst pain" item [Appendix 7], EQ-5D-5L [Appendix 9], and EORTC QLQ-BR23 [Appendix 6]) will be completed 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. Questionnaires are to be administered on Day 1 of Cycles 1, 2, and 3, Day 1 of every other cycle thereafter (i.e., Cycles 5, 7, 9, etc.), and at the treatment discontinuation visit. The QLQ-BR23 is to be given immediately after the QLQ-C30; male patients may be exempt from some of the questions included in the QLQ-BR23 module. For patients who discontinue study treatment for reasons other than disease progression, PRO assessments will continue to be administered according to the schedule of tumor assessments (i.e., every 8 weeks [±7 days] from randomization for the first 18 months, then every 12 weeks [±7 days] thereafter).

[v] The following PROs are to be completed 90 (±7) days after treatment discontinuation at a PRO follow-up visit (or via web-based system as required): BPI-SF "worst pain" item, EQ-5D-5L, and select scales of the QLQ-C30 (global health status/quality of life [Items 29 and 30], Physical Functioning [Items 1-5], Role Functioning [Items 6 and 7], pain [Items 9 and 19], fatigue [Items 10, 12, and 18], and dyspnea [Item 8]). This PRO follow-up visit is not applicable for patients who discontinue study treatment for reasons other than disease progression and who continue to be administered PROs according to the schedule of tumor assessments.

[w] Optional telephone interviews will be conducted with a subset of participants in the GDC-9545 arm at one timepoint following Cycle 2 (this can include the post-treatment period).

[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 treatment until the treatment discontinuation 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 30 days after the final dose of study drug. 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 exposure to study drug.

[z] Patients who are unwilling to return to the clinic for assessments after treatment discontinuation will no longer undergo adverse event and tumor response assessments at clinic visits but can undergo follow-up for adverse events, survival, and new anti-cancer therapy via telephone calls.

[aa] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

Appendix 2
Schedule of Pharmacokinetic Samples for Patients in GDC-9545 Arm

Table 1 Sparse PK Sample Collection[a]

Visit[a]	Timepoint	Sample Type
Day 1 of Cycles 1 and 2	Predose [b]	GDC-9545 PK (plasma)
	3 (+1) hours postdose	GDC-9545 PK (plasma)
Day 1 of Cycle 3, and Day 1 of every two cycles thereafter (e.g., Cycles 5, 7, 9, etc.) through Cycle 15	Predose [b]	GDC-9545 PK (plasma)
Treatment discontinuation visit	At any time during visit	GDC-9545 PK (plasma)

PK = pharmacokinetic.

Notes:

- Sparse PK samples will be collected from all patients in GDC-9545 arm.
- Actual dates and times must be recorded precisely for all doses and PK samples.
- Except for Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date.
- Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] All patients in GDC-9545 arm except subset of intensive PK patients.

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

Table 2 Intensive PK Sample Collection [a]

Visit	Timepoint	Sample Type
Day 1 of Cycles 1 and 2	Predose [b]	GDC-9545 PK (plasma)
	1, 2, 3, 4, and 6 hours (±15 minutes) postdose	GDC-9545 PK (plasma)
Day 1 of Cycle 3, and Day 1 of every two cycles thereafter (e.g., Cycles 5, 7, 9, etc.) through Cycle 15	Predose [c]	GDC-9545 PK (plasma)
Treatment discontinuation visit	At any time during visit	GDC-9545 PK (plasma)

PK = pharmacokinetic.

Notes:

- Intensive PK samples will be collected from a subset of patients in GDC-9545 arm.
- Actual dates and times must be recorded precisely for all doses and PK samples.
- Except for Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date.
- Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] Subset of intensive PK patients in GDC-9545 arm only. For intensive PK sample collection, approximately 40 patients (including 20 patients from mainland China during global enrollment phase and eventually extended China enrollment phase) will be enrolled in the GDC-9545 arm at selected sites to have approximately 16–24 PK-evaluable patients for GDC-9545 (8–12 patients globally and 8–12 patients from mainland China). Once this number has been obtained, sites will be informed that subsequently enrolled patients will not require intensive PK sampling.

[b] Same day as treatment administration (within 30 minutes before dosing).

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

Appendix 3
Schedule of Biomarker Samples

Visit	Timepoint	Sample Type
Screening Days –28 to –1	Any	Pretreatment archival or fresh tumor tissue sample [a]
Day 1 of Cycle 1	Predose	Plasma (somatic tumor mutations)
		Plasma (exploratory biomarker) [b]
		Blood (WGS or WES) [c]
Day 1 of Cycle 2	At any time during visit	Plasma (somatic tumor mutations)
		Plasma (exploratory biomarker) [b]
Day 1 of Cycle 3 and Day 1 of every two cycles thereafter (e.g., Cycles 5, 7, 9, etc.)	At any time during visit	Plasma (somatic tumor mutations) [b]
Treatment discontinuation visit	At any time during visit	Plasma (somatic tumor mutations)
		Plasma (exploratory biomarker) [b]
At disease progression (optional) [d]	Within 8 weeks of the progression assessment and prior to initiation of a new anti-cancer therapy	Fresh progression tumor tissue sample (optional) [d]

WGS = whole genome sequencing.

Notes: Except for Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] See Section 4.5.7 for details on tissue sample requirements.

[b] Not applicable in China.

[c] Not applicable for a site that has not been granted approval for WGS or WES. Not applicable in China (see Section 4.5.10). If missed for this time point, this blood sample for WGS or WES can be collected at any point in the study.

[d] Optional post-treatment tumor biopsy collected at time of disease progression for patients who have provided written informed consent and if collection of tumor biopsy sample is deemed clinically feasible (see Section 4.5.11). If possible, optional fresh biopsies should be obtained within 48 hours of the patient's final dose of study treatment, but no later than 8 weeks from the progression assessment and prior to initiation of subsequent anti-cancer therapy. Tumor biopsy of the growing lesion is preferred. Samples collected via resection, core-needle biopsy (minimum of three cores preferred), or excisional, incisional, punch or forceps biopsy are preferred. Not applicable in China.

Appendix 4
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

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

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area (e.g., brain metastases) or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as

possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is $\leq$5 mm. When CT scans have slice thickness of $>$5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$10 mm but $<$15 mm) should be considered non-target

lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

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

Recent literature indicates that vaccination-related adenopathy (enlarged lymph nodes) on radiologic imaging (e.g., CT, MRI) and transient uptake on PET scan are frequent findings (up to 16% in vaccine trials) after administration of COVID-19 vaccines. These findings may appear similar to malignant nodal involvement and hence impact image interpretation.

Measuring Lesions That Become Too Small to Measure

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used

for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and "too small to measure" should also be ticked).

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

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

  Any pathological lymph nodes must have reduction in short axis to <10 mm.

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

In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of $\geq$5 mm.

- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

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

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

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

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, 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 lesions in the face of SD or PR in target lesions 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 (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example,

necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE

Non-Target Lesions	New Lesions	Overall Response
Unequivocal PD	Yes or no	PD
Any	Yes	PD

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "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 lesions as shown in Table 2.

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

REFERENCES

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.

Appendix 5
European Organisation for Research and Treatment of Cancer QLQ-C30 Questionnaire (EORTC QLQ-C30)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study

Specimen

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Specimen

Appendix 6
European Organisation for Research and Treatment of Cancer QLQ-BR23 Questionnaire (EORTC QLQ-BR23)

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EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

Specimen

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Specimen

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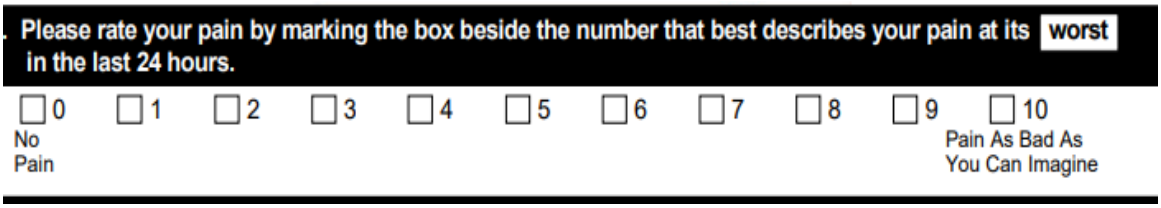
Appendix 7
Brief Pain Inventory–Short Form (BPI-SF) "Worst Pain" Item



Appendix 8
National Cancer Institute Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (NCI PRO-CTCAE) Items

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NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

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, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

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

SAMPLE

3.	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

4.	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

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

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

SAMPLE

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

Appendix 9
EQ-5D-5L

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Health Questionnaire

English version for the USA

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Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

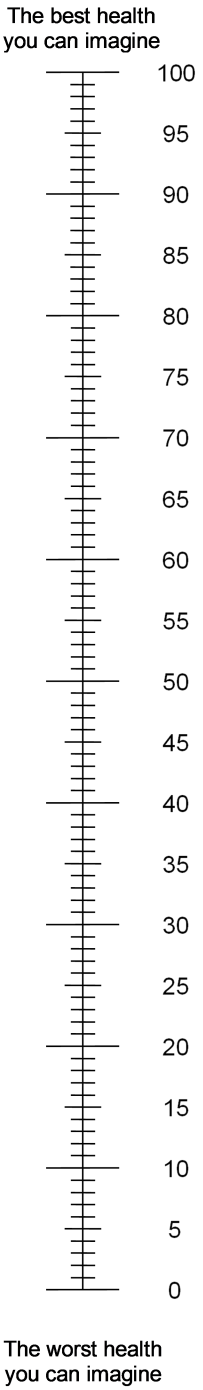
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 10
FACT-G Single-Item GP5, Overall Treatment Burden

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GP5 (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4

DRAFT

English (Universal)
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Appendix 11
Eastern Cooperative Oncology Group (ECOG) 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

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Approval Task	[redacted] Company Signatory 06-Dec-2022 14:04:48 GMT+0000