Official Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Inavolisib Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer

NCT Number: NCT04191499

Document Date: Protocol Version 8: 08-March-2023

PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF INAVOLISIB PLUS PALBOCICLIB AND FULVESTRANT VERSUS PLACEBO PLUS PALBOCICLIB AND FULVESTRANT IN PATIENTS WITH *PIK3CA*-MUTANT, HORMONE RECEPTOR–POSITIVE, HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	WO41554
VERSION NUMBER:	8
EUDRACT NUMBER:	2019-002455-42
IND NUMBER:	130909
NCT NUMBER	NCT04191499
TEST PRODUCT:	Inavolisib (RO7113755, GDC-0077)
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country and Region Protocols		
Version	**Date Final**	**Country and Region**	**Version**	**Date Final**
8	*See electronic date stamp on the final page of this document.*	—	—	—
7	*21 October 2022*	—	—	—
6	12 August 2022	—	—	—
4	3 November 2020	Canada	5	21 May 2021
—	—	VHP	3	4 August 2020
2	16 October 2019	VHP	2	16 October 2019
1	12 August 2019	VHP	1	12 August 2019

VHP = Voluntary Harmonization Procedure.

PROTOCOL AMENDMENT, VERSION *8*: RATIONALE

Protocol WO41554 Version 8 has been amended to redefine the study sample size due to the unanticipated slow enrollment experienced during the pandemic and is intended to minimize the risk of Last Patient In (LPI) occurring after the number of planned events for the primary PFS analysis is reached. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The total planned enrollment of 400 participants has been reduced to 320 to minimize the risk of LPI occurring after the number of planned events for the primary PFS analysis is reached. (Sections 3.1.1, 4.1, 6.1)
- The number of progression free survival events to trigger primary study readout has been reduced from 227 to 194, resulting in a change in the power of PFS from 90% to 85%, which is considered adequate for the primary endpoint (Sections 6, and 6.1).
- An interim and a final OS analysis were added to preserve the integrity of this key secondary study endpoint (Sections 6.4.2, 6.4.2.1, 6.9.1, 6.9.1.1).
- Non-investigational medicinal products were clarified (Section 4.3.3).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF INAVOLISIB PLUS PALBOCICLIB AND FULVESTRANT VERSUS PLACEBO PLUS PALBOCICLIB AND FULVESTRANT IN PATIENTS WITH *PIK3CA*-MUTANT, HORMONE RECEPTOR–POSITIVE, HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	WO41554
VERSION NUMBER:	8
TEST PRODUCT:	Inavolisib (RO7113755, GDC-0077)
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 to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF INAVOLISIB PLUS PALBOCICLIB AND FULVESTRANT VERSUS PLACEBO PLUS PALBOCICLIB AND FULVESTRANT IN PATIENTS WITH *PIK3CA*-MUTANT, HORMONE RECEPTOR–POSITIVE, HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	WO41554
VERSION NUMBER:	*8*
EUDRACT NUMBER:	2019-002455-42
IND NUMBER:	130909
NCT NUMBER	NCT04191499
TEST PRODUCT:	Inavolisib (RO7113755, GDC-0077)
PHASE:	III
INDICATION:	Breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of inavolisib (also known as "GDC-0077") in combination with palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant in patients with PIK3CA-mutant, hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. Specific objectives and corresponding endpoints for the study are outlined below.

Throughout this protocol, "study drug" refers to any of the individual agents assigned to patients as part of this study (i.e., inavolisib, placebo, palbociclib, or fulvestrant), while "study treatment" refers to the combination of agents assigned to patients as part of this study (i.e., inavolisib plus palbociclib and fulvestrant, or placebo plus palbociclib and fulvestrant).

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant 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 (RECIST), Version 1.1.

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoints:

- Objective response rate, defined as the proportion of patients with a complete response (CR) and/or partial response (PR) on at least two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1
- Best overall response rate, defined as the proportion of patients with a CR or PR, as determined by the investigator according to RECIST v1.1
- Duration of response, defined as the time from the first occurrence of a CR or PR 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
- Clinical benefit rate, defined as the proportion of patients with a CR, PR, and/or stable disease for at least 24 weeks, as determined by the investigator according to RECIST v1.1
- Overall survival (OS), defined as the time from randomization to death from any cause
- Time to deterioration (TTD) in pain, defined as the time from randomization to the first documentation of a ≥2-point increase from baseline on the "worst pain" item from the Brief Pain Inventory–Short Form (BPI-SF)
- TTD in Physical Function, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ-C30) Physical Function scale (items 1–5)
- TTD in Role Function, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-C30 Role Function scale (items 6 and 7)
- TTD in global health status (GHS)/health-related quality of life (HRQoL), defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-30 GHS/HRQoL scale (items 29 and 30)

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoints:

- Time to end of next-line treatment (proxy for time to second objective disease progression [PFS2]), defined as the time from randomization to end or discontinuation of next-line treatment, or death from any cause (whichever occurs first)
- Time to first skeletal-related event (SRE), defined as the time from randomization to the first occurrence of an SRE

  A SRE is a pathologic fracture, radiation therapy to bone, cancer-related surgery to bone, or spinal cord compression.
- Mean and mean change-from-baseline scores in all functions (Physical, Role, Cognitive, Emotional, and Social), GHS/HRQoL, and disease- or treatment-related symptom scores, as measured by the scales of the EORTC QLQ-C30 and EORTC QLQ–Breast Cancer Module 23 Questionnaire (EORTC QLQ-BR23)

Safety Objectives

The safety objective for this study is to evaluate the safety of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant 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

- Change from baseline in ECG parameters

The exploratory safety objective for this study is to evaluate the tolerability of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant from the patient's perspective, on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities (i.e., diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash symptoms) as assessed through use of the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument, as well as an additional item regarding the overall bother experienced due to side effects of treatment
- Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE and the additional bother item

Pharmacokinetic Objectives

The PK objective for this study is to characterize the pharmacokinetics of inavolisib, palbociclib, and fulvestrant, when administered in combination in this population, on the basis of the following endpoints:

- Plasma concentration of inavolisib at specified timepoints
- Plasma concentration of palbociclib at specified timepoints
- Plasma concentration of fulvestrant at specified timepoints

The exploratory PK objective is to evaluate potential relationships between the plasma exposure of inavolisib, palbociclib, and fulvestrant and efficacy and safety outcomes from this study.

The China-specific pharmacokinetic objective is to characterize the pharmacokinetics of inavolisib in all patients enrolled in China.

Biomarker Objective

The exploratory biomarker objective for this study are to identify and/or evaluate biomarkers that are associated with response and disease control with the study treatments, are early surrogates of efficacy of the study treatments, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with innate or acquired resistance to the study treatments, 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 activity of the study treatments (i.e., pharmacodynamic biomarkers), 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, 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 inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoint:

- Health utility and visual analog score of the European Quality of Life 5-Dimension, 5 Level (EQ-5D-5L) questionnaire

Study Design

Description of Study

Study WO41554 is a Phase III, randomized, double-blind, placebo-controlled, multicenter, global study designed to compare the efficacy, as measured by PFS, and the safety of the triplet combination of inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant in patients with *PIK3CA*-mutant, HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. Approximately *320* patients will be enrolled at approximately 200 global investigative sites.

Patients will be randomized to one of the following treatment arms in a 1:1 ratio:

Inavolisib plus palbociclib and fulvestrant

- Inavolisib: 9-mg tablet taken orally once a day (PO QD) on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1
- Palbociclib: 125-mg capsule or tablet taken PO QD on Days 1–21 of each 28-day cycle, beginning on Day 1 of Cycle 1
- Fulvestrant: 500 mg administered by intramuscular (IM) injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks.

Placebo plus palbociclib and fulvestrant

- Placebo: tablet taken PO QD on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1
- Palbociclib: 125-mg capsule or tablet taken PO QD on Days 1–21 of each 28-day cycle, beginning on Day 1 of Cycle 1
- Fulvestrant: 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks.

The study consists of a screening period of up to 28 days, a treatment period, a post-treatment follow-up period (which includes a "30-day safety follow-up" for all patients and, when applicable, a "post-treatment hyperglycemia follow-up," and/or a "post-treatment tumor assessment follow-up with patient-reported outcome [PRO] collection"), and a survival follow-up period.

Patients may be prescreened for *PIK3CA*-mutation status through central testing of circulating tumor DNA by participating in a separate prescreening consent. Patients may be re-screened only in cases of study-required assessments falling out of the screening window; all other screen failures are exclusionary.

Study treatment may continue until unequivocal disease progression as determined by the investigator, unacceptable toxicity, patient withdrawal of consent, or study termination.

Following study treatment discontinuation, patients will be followed for safety for 30 days after final study treatment (30-day safety follow-up, including a 30-day follow-up visit), or until the initiation of another anti-cancer therapy, whichever occurs first.

Patients on anti-hyperglycemic agents for the treatment of hyperglycemia during the study treatment period and those patients with events of hyperglycemia ongoing at the end of the 30-day safety follow-up, will undergo additional safety follow-up assessments ("post-treatment hyperglycemia follow-up") monthly until resolution of their fasting glucose to baseline levels, complete down-titration of their anti-hyperglycemic medications, or up to approximately 3 months after the final dose of study treatment, even if the patient initiates another anti-cancer therapy subsequent to study treatment discontinuation.

In addition, patients who discontinue active study treatment for reasons other than progression of disease or death will continue to have tumor assessments performed every 8 weeks (±7 days) for the first 2 years from randomization and every 12 weeks (±7 days) thereafter, and complete PRO assessments at those timepoints ("post-treatment tumor assessment follow-up with PRO collection"), until documented disease progression or the initiation of another anti-cancer therapy, whichever occurs first.

All patients will subsequently move onto the survival follow-up period until death, patient withdrawal of consent, loss to follow-up, or study termination.

Study patients must have measurable disease per RECIST v1.1. Patients with evaluable *(non-measurable)* bone-only disease are not eligible; *disease that is limited to bone but that has lytic or mixed lytic/blastic lesions and at least one measurable soft-tissue component (per RECIST v1.1) may be eligible*. Locally advanced disease must not be amenable to resection or other local therapy with curative intent.

Patients may enroll based on eligible *PIK3CA* mutation results from testing performed by a central investigational testing site or a site local test. Local testing of blood or tumor tissue must be performed using a Sponsor-approved polymerase chain reaction (PCR)-based or next-generation sequencing (NGS) assay at a Clinical Laboratory Improvement

Amendments (CLIA)- or equivalently-certified laboratory. Patients without available local test results for *PIK3CA* mutation status must submit a blood sample to determine whether an eligible *PIK3CA* mutation is present. Samples will be evaluated by the NGS-based FoundationOne® Liquid CDx ($F1LCDx$) assay, unless not implemented in specific localities. In this case, samples will be submitted to an alternative, Sponsor-designated central testing laboratory. Regardless of the testing strategy to determine a patient's tumor *PIK3CA* mutation status, all patients must provide both blood and tumor tissue for evaluation by a central investigational testing site. Demographic data will be collected on all patients who undergo screening, including those who screen fail.

Patients will be closely monitored for adverse events throughout the study treatment, and for 30 days after the final dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Adverse events will be graded according to NCI CTCAE v5.0. Patients who, at the 30-day safety follow-up visit, are still on anti-hyperglycemic agents for the treatment of hyperglycemia during the study treatment, and those patients with events of hyperglycemia ongoing at the 30-day safety follow-up visit, will go on to the post-treatment hyperglycemia follow-up (as defined above).

Tumor assessments will be performed to assess for response every 8 weeks ($\pm$7 days) during the first 2 years of study treatment and every 12 weeks ($\pm$7 days) thereafter. Patients who discontinue active study treatment for any reason other than unequivocal disease progression or death will follow the same tumor assessment schedule during the "post-treatment tumor assessment follow-up with PRO collection" period.

After study treatment discontinuation, all patients will be followed for survival and all subsequent anti-cancer therapies. These data will be collected via telephone calls and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

To evaluate the PK properties of GDC-0077, palbociclib, and fulvestrant administered in this triplet combination, blood samples will be taken at various timepoints before and after dosing.

Patient-reported outcome instruments will be completed by patients to evaluate the treatment impact from the patient's perspective as specified in the schedule of activities. The EORTC QLQ-C30 will assess disease and treatment-related symptoms often experienced by patients with locally advanced or metastatic cancer including fatigue, pain, depression/anxiety, and any limitations in function. The EORTC QLQ-BR23 will provide additional assessment on some treatment-related symptoms and symptoms that may occur with advanced disease. The "worst pain" item from the BPI-SF will be used to evaluate an increase in pain severity. Additionally, the PRO-CTCAE will be used to assess the impact of treatment-related symptoms, with the goal being to demonstrate benefit of treatment without adverse impact on patients' HRQoL. The EQ-5D-5L will be used to assess health status.

Mobile Nursing (MN) is only available at sites which have separately approved the use of the MN vendor; MN may not be conducted independently of the Sponsor-selected MN vendor. At applicable sites, study treatment may be administered and specified study assessments may be performed by a trained mobile nurse at the patient's home, if the patient has provided written informed consent to participate in MN visits.

Number of Patients

Approximately 320 patients with *PIK3CA*-mutant, HR-positive, HER2-negative locally advanced or metastatic breast cancer will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Women or men $\geq$18 years of age at time of signing Informed Consent Form

- If female, patients must meet at least one of the following definitions:

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

  Age ≥ 60 years

  Age < 60 years and 12 months of amenorrhea plus follicle-stimulating hormone and plasma or serum 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 to baseline)

  Premenopausal or perimenopausal (i.e., not meeting the criteria for postmenopausal) and meeting the following criterion:

  Treatment with luteinizing hormone–releasing hormone (LHRH) agonist therapy (e.g., goserelin or leuprolide) beginning at least 2 weeks prior to Day 1 of Cycle 1 and continuing for the duration of study treatment
- If male, recommendation of treatment with LHRH agonist therapy (e.g., goserelin or leuprolide) beginning at least 2 weeks prior to Day 1 of Cycle 1 and continuing for the duration of study treatment
- Histologically or cytologically confirmed adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to surgical or radiation therapy with curative intent
- Documented estrogen receptor-positive and/or progesterone receptor–positive tumor according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, defined as ≥1% of tumor cells stained positive based on the most recent tumor biopsy and assessed locally
- Documented HER2-negative tumor according to ASCO/CAP guidelines, defined as a HER2 immunohistochemistry (IHC) score of 0 or 1+, or an IHC score of 2+ accompanied by a negative fluorescence, chromogenic, or silver in situ hybridization test indicating the absence of *HER2* gene amplification, or a HER2/CEP17 ratio of <2.0 based on the most recent tumor biopsy and assessed locally
- Confirmation of biomarker eligibility: valid results from either central testing of blood or local testing of blood or tumor tissue documenting *PIK3CA*-mutant tumor status

  Eligible *PIK3CA* mutations are defined as follows:

H1047D/I/L/N/P/Q/R/T/Y	**G1049**A/C/D/R/S
E545A/D/G/K/L/Q/R/V	**E453**A/D/G/K/Q/V
E542A/D/G/K/Q/R/V	**K111**N/R/E
Q546E/H/K/L/P/R	**G106**A/D/R/S/V
N345D/H/I/K/S/T/Y	**G118**D
C420R	**R88**Q
M1043I/T/V	

  The central test for identification of eligible *PIK3CA* mutations is the $F1LCDx$ assay performed at Foundation Medicine, Inc. In localities where this is not available, samples will be submitted to an alternative, Sponsor-designated central testing laboratory.

  All patients are required to submit a freshly collected pre-treatment blood sample, whether patients are enrolled by local or central test results.

  Local tests of blood or tumor tissue may only be performed using a Sponsor pre-approved PCR- or NGS–based assay at a CLIA–certified or equivalent laboratory. The full laboratory report of the *PIK3CA* mutation result must be available and submitted for confirmation.

Local test results reported from blood should be from a blood specimen representative of patient's metastatic disease state, collected after conclusion of patient's most recent anti-cancer therapy.

Local test results reported from tumor tissue should be from the patient's metastatic disease state whenever possible.

- Consent to provide fresh (preferred) or archival tumor tissue specimen. It is preferred that the specimen be from the most recently collected and available tumor tissue, and whenever possible, from a metastatic site of disease. See the laboratory manual for specimen requirements.
- Patients must have progressed during adjuvant endocrine treatment or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen.

  If a cyclin-dependent kinase (CDK 4/6) inhibitor was included as part of neoadjuvant or adjuvant therapy, progression event must be >12 months since completion of CDK4/6 inhibitor portion of neoadjuvant or adjuvant therapy.
- Measurable disease per RECIST v1.1

  Patients with evaluable bone-only disease are not eligible; *disease that is limited to bone but has lytic or mixed lytic/blastic lesions and at least one measurable soft-tissue component per RECIST v1.1 may be eligible.*
- Treatment with endocrine-based therapy (e.g., palbociclib and fulvestrant) is recommended at time of entry into the study, as per national or local treatment guidelines
- For women of childbearing potential: 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 at least 60 days after the final dose of study treatment. Based on local prescribing information for fulvestrant, patients may be advised to use an effective means of contraception for up to 2 years after the final dose of fulvestrant. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, 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.

  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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 98 days after the final dose of study treatment to avoid exposing the embryo. Based on local prescribing information for fulvestrant, patients may be advised to use an effective means of contraception for up to 2 years after the final dose of fulvestrant. 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 acceptable methods of contraception. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Life expectancy of >6 months
- Adequate hematologic and organ function within 14 days prior to initiation of study treatment, defined by the following:

  Absolute neutrophil count $\geq 1500/\mu L$

  Hemoglobin ≥ 9 g/dL

  Platelet count $\geq 100{,}000/\mu L$

  Fasting glucose <126 mg/dL (<7.0 mmol/L) and HbA1c $<6.0\%$ (<42 mmol/mol)

  For patients with fasting glucose ≥ 100 mg/dL (≥ 5.5 mmol/L) (i.e., threshold for pre-diabetes) at baseline, recommend lifestyle changes according to American Diabetes Association guidelines; that is, dietary advice (e.g., small frequent meals, low carbohydrate content, high fiber, balanced carbohydrate intake over the course of the day, three small meals and two small snacks rather than one large meal) and exercise. Consultation with an endocrinologist or diabetologist is highly recommended.

  Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) ($<3 \times$ ULN if Gilbert's disease)

  Serum albumin ≥ 2.5 g/dL (25 g/L)

  AST and ALT $\leq 2.5 \times$ ULN with the following exception:

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

  Alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN with the following exception:

  Patients with documented liver or bone metastases may have ALP $\leq 5.0 \times$ ULN

  Creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation

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

  INR $<1.5 \times$ ULN and aPTT $<1.5 \times$ ULN

  For patients requiring anticoagulation therapy with warfarin or similar agents (such as Vitamin K antagonists), a stable INR between 2 and 3 is required. If anticoagulation is required for a prosthetic heart valve, then stable INR between 2.5 and 3.5 is permitted. Consult the local prescribing information for fulvestrant.

- Ability, in the investigator's judgment, and willingness to comply with all study-related procedures, including completion of patient-reported endpoints
- For patients enrolled in China: current resident of mainland China and must be of Chinese ancestry.

Exclusion Criteria

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

- Metaplastic breast cancer
- Any history of leptomeningeal disease or carcinomatous meningitis
- Any prior systemic therapy for metastatic breast cancer
- Prior treatment with fulvestrant or any selective estrogen-receptor degrader, with the exception of patients that have received fulvestrant or any selective estrogen-receptor degrader as part of neoadjuvant therapy only and with treatment duration of no longer than 6 months

- Prior treatment with any phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), or mammalian target of rapamycin (mTOR) inhibitor, or any agent whose mechanism of action is to inhibit the PI3K-AKT-mTOR pathway
- Appropriate for treatment with cytotoxic chemotherapy at time of entry into the study, as per national or local treatment guidelines (e.g., patients with visceral crisis)
- Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes
- Inability or unwillingness to swallow pills or receive IM injections
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:

  Measurable disease outside the CNS

  No ongoing requirement for corticosteroids as therapy for CNS metastases, with corticosteroids discontinued for $\geq$2 weeks prior to enrollment and no ongoing symptoms attributed to CNS metastases

  Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic assessments

  Screening CNS radiographic assessments $\geq$4 weeks since completion of radiotherapy

  No history of intracranial hemorrhage or spinal cord hemorrhage
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures biweekly or more frequently

  Indwelling pleural or abdominal catheters may be allowed, provided the patient has adequately recovered from the procedure, is hemodynamically stable and symptomatically improved.
- Serious infection requiring intravenous (IV) antibiotics within 7 days prior to Day 1 of Cycle 1
- Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
- Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye
- Requirement for daily supplemental oxygen
- Symptomatic active lung disease, including pneumonitis
- History of or active inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)

  Patients currently receiving immunosuppressants for inflammatory bowel disease (e.g., sulfasalazines) are considered to have active disease and are $thus$ ineligible.
- Any active bowel inflammation (including diverticulitis)
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

  Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.
- Clinically significant and active liver disease, including severe liver impairment (Child-Pugh Class B/C), viral or other hepatitis, current alcohol abuse, or cirrhosis

- Known HIV infection

  Sites should include an HIV test during screening, as allowed per local regulations.
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, metabolic, or infectious disease) or any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or that renders the patient at high risk from treatment complications
- Chemotherapy, radiotherapy, or any other anti-cancer therapy within 2 weeks before randomization
- Investigational drug(s) within 4 weeks before randomization
- Prior radiotherapy to $\geq$25% of bone marrow, or hematopoietic stem cell or bone marrow transplantation
- Unresolved toxicity from prior therapy, except for hot flashes, alopecia, and Grade$\leq$2 peripheral neuropathy
- History of other malignancy within 5 years prior to screening, except for cancers with very low risk of recurrence including, but not limited to, appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer. The Medical Monitor is available for consultation.
- History of or active clinically significant cardiovascular dysfunction, including the following:

  History of stroke or transient ischemic attack within 6 months prior to first dose of study treatment

  History of myocardial infarction within 6 months prior to first dose of study treatment

  New York Heart Association Class III or IV cardiac disease or congestive heart failure requiring medication

  Uncontrolled arrhythmias, history of or active ventricular arrhythmia requiring medication

  Coronary heart disease that is symptomatic or unstable angina

  Congenital long QT syndrome or QT interval corrected through use of Fridericia's formula $>$470 ms demonstrated by at least two ECGs $>$30 minutes apart, or family history of sudden unexplained death or long QT syndrome
- Clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Chronic corticosteroid therapy of $\geq$10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Allergy or hypersensitivity to components of the GDC-0077/placebo, palbociclib, or fulvestrant formulations
- Treatment with strong cytochrome P450 (CYP) 3A4 inducers or strong CYP3A4 inhibitors within 1 week or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
- Pregnant, lactating, or breastfeeding, or intending to become pregnant during the study or within 60 days after the final dose of study treatment (based on local prescribing information for fulvestrant, patients may be advised to use an effective means of contraception for up to 2 years after the last dose of fulvestrant)

  Women of childbearing potential (including those who have had a tubal ligation) must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Major surgical procedure, or significant traumatic injury, within 28 days prior to Day 1 of Cycle 1 or anticipation of the need for major surgery during the course of study treatment
- Minor surgical procedures $<$7 days prior to first dose of study treatment

Patients must have sufficiently recovered from surgery, including adequate wound healing.

End of Study

The end of this study 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 safety follow-up is received from the last patient, whichever occurs later.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6 years.

Investigational Medicinal Products

Test Products (Investigational Drug)

The investigational medicinal products for this study are inavolisib or its placebo, palbociclib, and fulvestrant. Inavolisib 9-mg tablet is taken PO QD on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1. Placebo tablet is taken PO QD on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1. Palbociclib 125-mg capsule or tablet is taken PO QD on Days 1–21 of each 28-day cycle, beginning on Day 1 of Cycle 1. Fulvestrant 500 mg is administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks.

Non-Investigational Medicinal Products

LHRH Agonists

Luteinizing hormone–releasing hormone agonists are required beginning at least 2 weeks prior to initiation of study treatment for pre-/peri-menopausal women. For male patients, LHRH agonist therapy beginning at least 2 weeks prior to initiation of study is recommended. Acceptable agents include goserelin or leuprolide; triptorelin is also acceptable. Patients already on one of these three agents may remain on the same agent without switching. Every effort should be made to administer goserelin (given every 28 days) or alternative LHRH agonist as applicable on site at the time of fulvestrant administration in order to minimize the number of clinic visits. Where allowed per local standards, patients receiving LHRH agonists should be monitored (via follicle-stimulating hormone and/or estradiol level, as per local standards) approximately every 3 months for appropriate hormonal suppression; in cases of inadequate suppression, alternative hormonal suppression methods (e.g., ovarian ablation, as per local standards) must be considered.

Dexamethasone Mouth Rinse

If locally available, a compounded alcohol-free mouthwash of dexamethasone (0.5 mg in 5 mL) is recommended for prophylaxis or treatment of stomatitis/mucositis. As per the SWISH study (Rugo et al. 2017), patients may use 4 times daily for 8 weeks (10 mL swished for 2 minutes and spat) started concurrently with study treatment and/or used reactively with the first appearance of symptoms. No food or drink should be consumed for at least 1 hour after swishing and spitting the mouthwash. Additional mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal, and/or antibiotics) or topical corticosteroids (e.g., triamcinolone acetonide 0.05%–0.5%, fluocinolone acetonide 0.025%–0.05%, clobetasol propionate 0.025%) may be implemented. Diet should be modified (e.g., avoidance of spicy foods) and harsh mouthwashes (e.g., Listerine®) should be avoided.

Metformin

Patients experiencing hyperglycemia may require anti-hyperglycemic medication. The preferred first agent is metformin. At the investigator's discretion and where allowed by local regulations, prophylactic metformin may be initiated on Cycle 1, Day 1 for patients at high risk of hyperglycemia.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoint:

- Progression free survival, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), according to RECIST v1.1

Data for patients without the occurrence of disease progression or death will be censored at the time of the last tumor assessment (or at the time of randomization if no tumor assessment was performed after the baseline visit).

The primary efficacy analysis population will consist of all randomized patients grouped according to their assigned treatment at randomization.

The primary analysis of the study will test the equality of PFS distributions in the inavolisib plus palbociclib and fulvestrant and placebo plus palbociclib and fulvestrant arms, as follows:

H0: PFS inavolisib plus palbociclib and fulvestrant = PFS placebo plus palbociclib and fulvestrant

versus

H1: PFS inavolisib plus palbociclib and fulvestrant ≠ PFS placebo plus palbociclib and fulvestrant

The treatment arms will be compared using a two-sided stratified log-rank test. The stratification factors that will be used are the same as those for randomization:

- Visceral disease (yes or no)
- Endocrine resistance
  (primary or secondary according to European Society for Medical Oncology Advanced Breast Cancer 4 guidelines [Cardoso et al. 2018])
- Geographic region (North American/Western Europe, Asia, or other)

The results from the unstratified log-rank test also will be provided.

Survival curves in each treatment arm will be estimated using Kaplan-Meier estimates. The Kaplan-Meier estimates will provide a visual description of the survival curves and the difference across treatment arms. In addition, the Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The treatment effect will be quantified via a hazard ratio, computed from a stratified Cox proportional-hazards regression, including a 95% confidence interval.

Sensitivity analyses will be conducted including only patients whose tumor *PIK3CA* mutation status has been confirmed centrally in blood and based on independent central review of response. Further sensitivity analyses are defined in the Statistical Analysis Plan (SAP).

Determination of Sample Size

Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- Two-sided log-rank test at the 0.05 level of significance
- $Eighty\text{-}five\ percent$ power to detect a hazard ratio for inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant of 0.65, corresponding to an improvement in median PFS from 11 to 16.9 months
- Exponential distribution of PFS
- An annual dropout rate of 15%

With these assumptions, 194 PFS events are required to achieve 85% power for the primary analysis. The 320 patients will be enrolled over approximately 43 months and the primary analysis is expected to occur $approximately\ 50\ months$ after the first patient randomized.

The minimal detectable difference for the PFS hazard ratio is 0.754 (i.e., an improvement of 11 to 14.6 months in median PFS).

Of the 320 patients, no more than 60 patients will be allowed to have a *PIK3CA* tumor mutation not confirmed by the central F1LCDx assay. As such, at least 260 patients will have the presence of (one or more) *PIK3CA* mutation(s) confirmed by the central F1LCDx assay.

Interim Analyses

An independent Data Monitoring Committee will convene to review cumulative safety data approximately every 4 months.

One interim analysis for futility will be conducted after approximately 75 PFS events (33% of information) are observed. The futility boundary is non-binding. The cutoff is expected to occur 18 months after first patient enrolled and, hence, approximately 265 patients will have been enrolled when the decision is available.

As an additional safety monitoring measure, an interim safety review will be performed after the enrollment of the first 25 patients and treatment for at least three cycles.

One interim analysis will be performed for OS at the time of the primary endpoint analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	Advanced Breast Cancer
AE	adverse event
AESI	adverse events of special interest
AKT	protein kinase B
ALP	alkaline phosphatase
ASCO	American Society of Clinical Oncology
AUC	area under the concentration-time curve
BICR	blinded independent central review
BOR	best overall response rate
BPI-SF	Brief Pain Inventory-Short Form
CAP	College of American Pathologists
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CI	confidence interval
ctDNA	circulating tumor DNA
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration observed
CNA	copy number alteration
COVID-19	*coronavirus disease 2019*
CR	complete response
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CV	*coefficient of variation*
CYP	cytochrome P450
DDI	drug–drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life–Breast Cancer Module 23 Questionnaire
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire
EQ-5D-5L	European Quality of Life 5-Dimension, 5 Level Questionnaire

Abbreviation	Definition
ESMO	European Society for Medical Oncology
ER	estrogen receptor
F1LCDx	FoundationOne® Liquid CDx
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FMI	*Foundation Medicine, Inc.*
GHS	global health status
HbA1c	glycosylated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HER2	human epidermal growth factor 2
HR	hormone receptor
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
iDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IM	intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice or web-based response system
LHRH	luteinizing hormone–releasing hormone
MN	mobile nursing
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NaF	sodium fluoride
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
NGS	next-generation sequencing
ORR	overall response rate
OS	overall survival
p110α	alpha isoform of PI3K
pAKT	phosphorylated form of protein kinase B

Abbreviation	Definition
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PF	physical functioning
PFS	progression-free survival
PFS2	second objective disease progression
PI3K	phosphatidylinositol 3-kinase
PIK3CA	phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform [gene name/acronym]
PIP_2	phosphatidylinositol 4,5-bisphosphate
PIP_3	phosphatidylinositol 3,4,5-bisphosphate
PK	pharmacokinetic
PO	orally
PopPK	population PK
pPRAS40	PRAS40 phosphorylated at Threonine 246
PR	partial response
PRO	patient-reported outcome
pS6RP	S6RP phosphorylated at Serine 235/236
PTEN	phosphatase and tensin homolog
QD	once a day
QoL	*quality of life*
Rb	*retinoblastoma* protein
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RF	role functioning
SAP	Statistical Analysis Plan
SD	stable disease
SGLT2	sodium glucose co-transporter 2
SmPC	Summary of Product Characteristics
SRE	skeletal-related event
TL	target lesion
TMB	tumor mutational burden
TTD	time to deterioration
ULN	upper limit of normal
USPI	U.S. Package Insert
VAS	visual analog *score*
WES	whole exome sequencing

Abbreviation	Definition
WGS	whole genome sequencing
WT	wild type

1. BACKGROUND

1.1 BACKGROUND ON HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE ADVANCED OR METASTATIC 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). Breast cancer in men is rare; in 2019 $<1\%$ of new breast cancer diagnoses in the United States occurred in men (American Cancer Society 2019).

Hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative breast cancer accounts for 60%–70% of all breast cancers. Current treatments for advanced or metastatic disease focus on prolonging life and improving or maintaining quality of life. Preventing resistance to therapy and ultimately achieving a cure remain unmet needs in this disease setting.

Standard-of-care treatment options for patients with de novo metastatic disease, or for whom disease recurs following surgery and adjuvant treatment, include endocrine therapy, endocrine and targeted therapy combinations, or chemotherapy (National Comprehensive Cancer Network [NCCN] 2019). Chemotherapy is indicated in patients with symptomatic visceral disease or in patients with disease progression after multiple consecutive endocrine therapy regimens (NCCN 2019). For most patients, endocrine therapy alone or in combination with a targeted therapy is the treatment of choice in the metastatic setting.

Endocrine therapy options for the treatment of postmenopausal women with locally advanced or metastatic HR-positive breast cancer include nonsteroidal aromatase inhibitors (anastrozole, letrozole), steroidal aromatase inhibitors (exemestane), estrogen receptor (ER) downregulators (fulvestrant), and ER modulators (tamoxifen, toremifene). In premenopausal women, ovarian ablation or suppression is also generally recommended.

Not all HR-positive breast cancers respond optimally to endocrine therapy. Multiple mechanisms may lead to primary and/or secondary resistance to endocrine therapy in HR-positive breast cancer including upregulation of growth factor signaling pathways, such as the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway (Johnston 2009; Musgrove and Sutherland 2009). The addition of targeted therapies to endocrine therapy may be able to overcome mechanisms of resistance to endocrine therapy.

Recent data from Phase III studies have demonstrated significant improvements in progression-free survival (PFS) with the addition of targeted therapies to endocrine therapy, leading to new standard-of-care treatment options. The BOLERO-2 trial demonstrated that the addition of an mTOR inhibitor, everolimus, to exemestane significantly improved PFS in postmenopausal patients with ER-positive advanced

breast cancer who had experienced recurrence or progression of disease while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting and/or for advanced disease (Baselga et al. 2012; Yardley et al. 2013).

Cyclin-dependent kinases (CDKs) are key regulators of cell-cycle progression. The cellular transition from G1 phase to S phase, commonly referred to as the restriction point, is controlled by the interaction of cyclin D and CDKs 4 and 6 (CDK4/6). CDK4 and CDK6 phosphorylate the retinoblastoma (Rb) protein, leading to the activation of E2F transcription factors that initiate S phase gene expression, thereby promoting cell-cycle progression. Amongst others, palbociclib is a CDK4/6 inhibitor that has been evaluated in combination with endocrine therapy in multiple clinical trials.

Data from the Phase III PALOMA-2 study confirms the findings of the randomized Phase II study PALOMA-1 (Finn et al. 2015, 2016). In PALOMA-2, 666 postmenopausal patients with HR-positive, HER2-negative advanced breast cancer who had received no prior treatment for advanced disease were randomized in a 2:1 ratio to the combination of palbociclib (125 mg orally [PO] once a day [QD] on Days 1–21 of 28-day cycles) and letrozole (2.5 mg PO QD on Days 1–28 of 28-day cycles) or to placebo and letrozole. The primary endpoint of investigator-assessed PFS in the intent-to-treat (ITT) population demonstrated a significant improvement in PFS from 14.5 months with placebo and letrozole to 24.8 months with palbociclib and letrozole (hazard ratio: 0.58). Objective response rate (42% vs. 35%), clinical benefit rate (CBR; 85% vs. 70%), and median duration of response (DOR; 23 months vs. 17 months) all favored palbociclib and letrozole over placebo and letrozole. In addition, significantly greater improvement in pain scores was observed in the palbociclib and letrozole arm (Rugo et al. 2018). Toxicity observed with palbociclib and letrozole was similar to other Phase II and III studies of palbociclib and endocrine therapy, with Grade 3 or 4 neutropenia occurring in 66% of patients. Dose interruptions, cycle delays, and $\geq$1 dose reduction were common, occurring in 70%, 68%, and 36% of patients treated with palbociclib and letrozole, respectively. Permanent discontinuation for adverse events was 9.7% in the palbociclib and letrozole treatment arm, compared with 5.9% in the placebo and letrozole treatment arm.

In the Phase III PALOMA-3 study, 521 patients with advanced HR-positive, HER2-negative breast cancer that had relapsed or progressed during prior endocrine therapy were randomized 2:1 to palbociclib and fulvestrant or to placebo and fulvestrant (Turner et al. 2015). After a median follow-up of 8.9 months, ORR (19% vs. 9%), CBR (67% vs. 40%), and median PFS (9.5 months vs. 4.6 months) all favored palbociclib and fulvestrant over placebo and fulvestrant. Significantly greater improvement from baseline in pain was observed in the palbociclib and fulvestrant arm (Harbeck et al. 2016). Toxicity observed with palbociclib and fulvestrant was similar to other Phase II and III studies of palbociclib and endocrine therapy, with the following Grade 3 or 4 hematological adverse events: neutropenia, 65%; anemia, 3%; and thrombocytopenia, 3%. Febrile neutropenia occurred in 0.9% of patients. Permanent

discontinuation for adverse events was 4% in the palbociclib and fulvestrant treatment arm compared with 2% in the placebo and fulvestrant treatment arm (Cristofanilli et al. 2016). After a median follow-up of 44.8 months, median OS also favored palbociclib and fulvestrant over placebo and fulvestrant (34.9 months vs. 28.0 months, stratified hazard ratio for death 0.81) (Turner et al. 2018).

Thus, the addition of targeted therapy to endocrine therapy has demonstrated improvement in PFS, although with additional toxicity over endocrine therapy alone. Predictive biomarkers to identify patients most likely to derive the greatest benefit from the combination of endocrine and targeted therapies remain limited.

Approximately 40% of patients with HR-positive breast cancer have tumors that harbor mutations in *PIK3CA*, the gene encoding the catalytic subunit of the alpha isoform of PI3K (p110α). These mutations result in upregulation of PI3K pathway activity (Saal et al. 2005; Stemke-Hale et al. 2008) and sensitize nonclinical models to inhibition with selective PI3K inhibitors (O'Brien et al. 2010; Schleifman et al. 2014). A number of PI3K inhibitors are in clinical development for the treatment of HR-positive breast cancer, and one, alpelisib, has recently been approved in the United States in combination with fulvestrant for treatment of HR-positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.

The specificity of inavolisib (also known as GDC-0077) for the PI3Kα isoform, together with its unique mechanism of action that leads to specific degradation of mutant p110α, should enable a broad therapeutic index as a single agent and in combination with standard-of-care endocrine and targeted therapies.

Improved treatment options in HR-positive, HER2-negative breast cancer may decrease or eliminate the risk of late recurrences after adjuvant therapy, provide more tolerable effective treatment options, and ultimately achieve a cure for patients with advanced disease. Maximizing therapeutic benefit, while minimizing treatment-related toxicities, is particularly important in HR-positive, HER2-negative breast cancer where treatment duration can be long.

1.2 BACKGROUND ON THE PI3K/AKT/MTOR PATHWAY AND BREAST CANCER

Phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), and mammalian target of rapamycin (mTOR) are major nodes in the PI3K/AKT/mTOR intracellular signaling pathway and are critical for cell-cycle modulation, cell growth, metabolism, motility, and survival (Cantrell 2001; Hanahan and Weinberg 2011; Vanhaesebroeck et al. 2012). The PI3K/AKT/mTOR pathway is generally activated following ligand-receptor tyrosine kinase interactions. Under physiologic conditions, the main role of PI3K is to facilitate the metabolism of inositol phospholipids for intracellular signal transduction.

There are three classes of PI3K, with Class I being the most responsive to external stimuli. Class I PI3Ks are composed of two subunits: a p110 catalytic subunit and a regulatory adapter subunit, p85. There are four isoforms of the p110 catalytic subunit of PI3K: α, β, γ, and δ. These four isoforms are the respective products of the genes *PIK3CA*, *PIK3CB*, *PIK3CG*, and *PIK3CD*. *PIK3CA* and *PIK3CB* are expressed in all cells, while *PIK3CD* is primarily expressed in leukocytes and *PIK3CG* is expressed in multiple tissues, including pancreas, skeletal muscle, liver, and heart.

Dysregulation of the PI3K/AKT/mTOR signaling pathway has been described in multiple solid tumor malignancies: glioblastoma, colorectal, gastric, lung, endometrial, ovarian, prostate, and breast cancers (Gustin et al. 2008). Pathway activation may occur through multiple mechanisms: loss of the tumor suppressor phosphatase and tensin homolog (PTEN), amplification or somatic mutations in *PIK3CA*, mutations in AKT, mutations in the regulatory subunit p85, mutations and/or amplification of upstream-receptor tyrosine kinases, mutations in RAS, and loss of liver kinase B1, type II inositol polyphosphate-4-phosphatase, or tuberous sclerosis (Staal 1987; Cheng et al. 1992; Bellacosa et al. 1995; Li et al. 1997; Steck et al. 1997; Aoki et al. 1998). Activating mutations in the *PIK3CA* gene are the most common genomic alterations and occur primarily in exons 9 and 20 (“hotspot” regions), which encode the helical and kinase domains of the PI3Kα protein (Bachman et al. 2004; Samuels et al. 2004).

Up to 70% of breast cancers can have some form of molecular aberration of the PI3K/AKT/mTOR pathway (Cancer Genome Atlas Network 2012). Hyperactivation of the PI3K/AKT/mTOR signaling pathway was proven to promote both de novo and acquired resistance to hormone therapy in ER-positive breast cancer cell lines and xenograft models (Sabnis et al. 2007), and simultaneous blocking of the PI3K/AKT/mTOR pathway with everolimus and the ER pathway with letrozole results in greater anti-tumor activity than either agent alone (Boulay et al. 2005). In addition, evidence of baseline PI3K activation was found to be predictive of a poor prognosis after adjuvant endocrine therapy (Miller et al. 2010).

These data provide support for the hypothesis that blocking PI3K/AKT/mTOR pathway signaling may have a therapeutic benefit in patients with ER-positive, HER2-negative breast cancer.

In the clinical setting, results of the combination of exemestane and everolimus, an mTOR inhibitor, were reported in the BOLERO-2 trial (Baselga et al. 2012). This study compared everolimus and exemestane with placebo and exemestane in 724 postmenopausal patients with ER-positive advanced breast cancer who had experienced recurrence or progression of disease while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting and/or for advanced disease. Median PFS in the everolimus group was 6.9 months compared with 2.8 months in the placebo group. The hazard ratio for PFS by investigator assessment was

0.43 (95% confidence interval [CI]: 0.35 to 0.54; $p < 0.001$). The magnitude of the effect was even greater with central independent review: hazard ratio = 0.36 (95% CI: 0.27 to 0.47; $p < 0.001$).

An important finding in studies with mTOR-targeting drugs such as everolimus is that these drugs produce a pharmacodynamic paradox: while inhibiting mTOR, the administration of these drugs leads to an upregulation of the phosphorylated form of AKT (pAKT), resulting in feedback PI3K/AKT/mTOR pathway activation (Tabernero et al. 2008). This finding suggests that alternative pharmacologic strategies to effectively shut down the pathway upstream of AKT should be pursued.

One of these strategies is inhibiting the PI3K/AKT/mTOR pathway with agents that specifically target PI3K. One such example is alpelisib, a molecule that primarily inhibits PI3Kα. The recently reported SOLAR-1 trial (André et al. 2019) studied alpelisib in combination with fulvestrant in HR-positive, HER2-negative advanced or metastatic breast cancer. Based on study results, the U.S. Food and Drug Administration (FDA) has approved the use of alpelisib in combination with fulvestrant for the treatment of HR-positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. In the cohort of 341 patients with *PIK3CA*-mutated cancer, PFS at a median follow-up of 20 months was 11.0 months (95% CI: 7.5 to 14.5 months) in the alpelisib plus fulvestrant group, as compared with 5.7 months (95% CI: 3.7 to 7.4 months) in the placebo plus fulvestrant group (hazard ratio = 0.65; 95% CI: 0.50 to 0.85; $p < 0.001$). This provides clinical validation of the addition of PI3K inhibition to endocrine therapy in this disease space.

This therapy is accompanied, however, by significant toxicities. Among all patients in SOLAR-1 (n = 571), the most frequent Grade 3 or 4 adverse events were hyperglycemia (36.6% in the alpelisib plus fulvestrant group vs. 0.7% in the placebo plus fulvestrant group) and rash (9.9% vs. 0.3%). Grade 3 diarrhea occurred in 6.7% versus 0.3% of patients. Twenty-five percent of patients treated with alpelisib permanently discontinued treatment due to adverse events versus 4.2% in the placebo arm.

1.3 BACKGROUND ON INAVOLISIB

Inavolisib (also known as “GDC-0077”) is a potent and selective inhibitor of the Class I PI3Kα isoform, with > 300-fold less potent biochemical inhibition of other Class I PI3Ks, including the β, δ, and γ isoforms, and with increased potency in tumor cells bearing mutant p110α over cells bearing wild type (WT) p110α. Inavolisib exerts its activity by binding to the adenosine 5′-triphosphate binding site of p110α, thereby inhibiting the phosphorylation of membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphophate (PIP_3). Inhibiting the phosphorylation of PIP_2 to PIP_3 decreases downstream activation of pathway effectors including AKT and S6RP, resulting in decreased cellular proliferation, metabolism, and angiogenesis. Nonclinical studies demonstrate that inavolisib specifically degrades mutant p110α, inhibits proliferation and induces apoptosis in *PIK3CA*-mutant breast cancer cell lines, inhibits

tumor growth in human breast cancer xenograft models harboring *PIK3CA* mutations, and reduces downstream PI3K pathway markers, including pAKT, PRAS40 phosphorylated at Threonine 246 (pPRAS40), and S6RP phosphorylated at Serine 235/236 (pS6RP).

1.3.1 Nonclinical Data for Inavolisib

Results of in vitro combination studies indicate positive combination effects between inavolisib and endocrine therapies and between inavolisib and palbociclib. In the *PIK3CA*-mutant, ER-positive breast cancer cell line, MCF-7, inavolisib alone caused growth inhibition. Effects on growth were also observed with fulvestrant and palbociclib when administered as single agents. Combined treatment of cells with inavolisib and fulvestrant caused dose-dependent inhibition of cell viability at lower concentrations compared with either inavolisib or fulvestrant alone. In addition, treatment with inavolisib and palbociclib yielded similar in vitro combination effects with increased dose-dependent inhibition of cell viability compared with either inavolisib or palbociclib alone.

In vivo anti-tumor activity of inavolisib was established using human tumor xenograft models that harbor hotspot mutations in *PIK3CA*. Anti-tumor activity was evaluated as percentage of tumor growth inhibition relative to vehicle controls for inavolisib as a single agent or in combination with either chemotherapeutics or targeted agents. These in vivo studies demonstrated that inavolisib has robust anti-tumor activity as a single agent and improved efficacy when administered in combination with marketed anti-cancer agents, including fulvestrant (endocrine therapy), palbociclib (CDK4/6 inhibitor), and paclitaxel (chemotherapy), in the MCF-7 human breast cancer xenograft model, which harbors the E545K hotspot mutation in *PIK3CA*. PI3K pathway markers, including pAKT, pPRAS40, and pS6RP, were reduced for up to 8 hours in response to a single dose of inavolisib.

The nonclinical safety of inavolisib has been assessed in a comprehensive battery of toxicology studies which include single-dose and repeat-dose general toxicology studies (QD PO dosing) of up to 3 months duration in rats and dogs; in vitro and in vivo genetic toxicology studies; in vitro phototoxicity study; in vitro and in vivo secondary pharmacology and safety pharmacology studies; and embryofetal development (Segment II) studies in rats.

The dose limiting toxicities (DLTs) identified in nonclinical toxicology studies were consistent with the anticipated pharmacologic effects of PI3K inhibition, and included hyperglycemia and body weight loss in rats and dogs, and inflammation in dogs. In addition, bone marrow hypocellularity, atrophy of glandular and reproductive tissues and eye lens degeneration were observed in the rats; and lymphoid depletion and swelling of the lens fibers in the eye were observed in the dogs. Findings were generally dose-dependent and reversible, and/or considered to be clinically monitorable and/or manageable.

In vitro and in vivo safety pharmacology studies of inavolisib demonstrated a low risk for adverse cardiovascular, neurologic, and respiratory effects at clinically relevant exposures. Inavolisib is considered to have no phototoxic potential.

Inavolisib was not mutagenic in the bacterial mutagenesis assay. Inavolisib showed in vitro clastogenicity at high concentrations in human peripheral blood lymphocytes; however, there was no evidence of inavolisib-induced clastogenicity, aneugenicity, or DNA damage in a subsequent in vivo micronucleus and alkaline comet study in rats up to maximum tolerated dose of 40 mg/kg (~15.8× of clinical exposure at 9 mg).

Fetal malformations and variations observed in rats warrant the continued use of highly effective contraception in clinical trials. *Refer to* the Inavolisib Investigator's Brochure for more detailed information.

1.3.2 Clinical Data for Inavolisib

In the Phase I Study GO39374, 157 patients with *PIK3CA*-mutant metastatic tumors were enrolled and treated (as of the clinical cutoff date of 20 March 2020): 156 patients with breast cancer and 1 patient with colorectal cancer. These patients were enrolled into one of six arms:

- Arm A: GDC-0077 single agent, dose escalation
- Arm B: GDC-0077 (9 mg QD) plus palbociclib and letrozole, dose escalation and expansion
- Arm C: GDC-0077 (9 mg QD) plus letrozole, dose escalation and expansion
- Arm D: GDC-0077 (9 mg QD) plus fulvestrant, expansion
- Arms E and F: GDC-0077 (9 mg QD) plus palbociclib and fulvestrant (Arm E) and with metformin *for patients with obesity or pre-diabetes* (Arm F), expansion

Enrollment was ongoing in the expansion stage at the GDC-0077 9 mg QD dose level in Arms D, E, and F at the clinical cutoff date.

In Arm A of GO39374, among 20 patients with measurable disease treated with 6-mg, 9-mg, or 12-mg QD starting dose of GDC-0077 as a single agent, 5 patients (25%) achieved partial responses (PRs), while 9 patients (45%) achieved clinical benefit (defined as the percentage of patients achieving confirmed Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.1 defined complete response [CR], PR, and/or stable disease [SD] [non-complete response/non-progressive disease for patients with non-measurable disease at baseline]≥24 weeks). Of these, all were at the 6-mg or 9-mg QD starting dose, and 3 patients had received prior CDK4/6 inhibitor therapy. Patients in Arm A also had ^{18}F-fluorodeoxyglucose-positron emission tomography scans at baseline and after 2 weeks of QD GDC-0077 dosing to evaluate changes in glucose metabolism as a marker of PI3K pathway modulation. At 6 mg, 9 mg, and 12 mg, respectively, 4 of 7 patients (57%), 6 of 9 patients (67%), and 2 of 4 patients (50%) were

metabolic responders by STARCIST criteria (Bengtsson et al. 2015) with mean percent decreases in maximum standard uptake value of 25.3%, 43.4%, and 41.5%.

In Arm B, among 33 patients with measurable disease treated with 3-mg, 6-mg, or 9-mg QD starting dose of GDC-0077 in combination with palbociclib and letrozole, 14 patients (42%) achieved PRs, and 1 patient (3%) achieved CR; in addition, 26 patients (79%) achieved clinical benefit (defined as the percentage of patients achieving confirmed RECIST v1.1 defined CR, PR, and/or SD [non-complete response/non-progressive disease for patients with non-measurable disease at baseline] ≥24 weeks). Of these, 30 patients were at the 6-mg or 9-mg QD starting dose, and 2 patients had received prior CDK4/6 inhibitor therapy.

In Arm C, among 37 patients with measurable disease treated with 6-mg or 9-mg QD starting dose of GDC-0077 in combination with letrozole, 6 patients (16%) achieved PRs, while 13 patients (35%) achieved clinical benefit (defined as the percentage of patients achieving confirmed RECIST v1.1 defined CR, PR, and/or SD [non-complete response/non-progressive disease for patients with non-measurable disease at baseline] ≥24 weeks). Of these, 30 patients were at the 9-mg QD starting dose, and 4 patients had received prior CDK4/6 inhibitor therapy.

In Arm D, among 39 patients with measurable disease treated with 9-mg QD starting dose of GDC-0077 in combination with fulvestrant, 6 patients (15%) achieved PRs, while 16 patients (41%) achieved clinical benefit (defined as the percentage of patients achieving confirmed RECIST v1.1 defined CR, PR, and/or SD [non-complete response/non-progressive disease for patients with non-measurable disease at baseline] ≥24 weeks). Of these, 4 patients had received prior CDK4/6 inhibitor therapy.

In Arm E, among 13 patients treated with 9-mg QD starting dose of GDC-0077 in combination with palbociclib and fulvestrant, 5 patients (39%) achieved PRs, while 8 patients (62%) achieved clinical benefit (defined as the percentage of patients achieving confirmed RECIST v1.1 defined CR, PR, and/or SD [non-complete response/non-progressive disease for patients with non-measurable disease at baseline] ≥24 weeks).

In Arm F, among 15 patients treated with 9-mg QD starting dose of GDC-0077 in combination with palbociclib and fulvestrant and prophylactic metformin, two patients (13%) achieved PRs, while 9 patients (60%) achieved clinical benefit (defined as the percentage of patients achieving confirmed RECIST v1.1 defined CR, PR, and/or SD [non-complete response/non-progressive disease for patients with non-measurable disease at baseline] ≥24 weeks).

Overall, adverse events occurring in≥20% of patients, regardless of attribution, included diarrhea (63%), hyperglycemia (62%), nausea (52%), vomiting (32%), neutropenia (31%), decreased appetite (31%), fatigue (28%), stomatitis (26%),

anemia (25%), dysgeusia (25%), headache (25%), alopecia (22%), cough (22%), and constipation (20%). Grade ≥3 adverse events occurring in ≥4 patients (2.5%), regardless of attribution, included hyperglycemia and neutropenia (23% each; neutropenia included terms of neutropenia and neutrophil count decreased), anemia (6%), AST increased, lymphopenia, fatigue, hypokalemia, and hypophosphatemia (5% each), leukopenia, and nausea (4% each), ALT increased, hypercalcemia, thrombocytopenia, and hyponatremia (3% each). Hyperglycemia is anticipated with PI3Kα inhibition, and events were manageable with oral anti-hyperglycemic agents. Diarrhea was mild (all events Grade 1 or 2). Other PI3K-inhibition associated adverse events observed included grouped terms for stomatitis (45% all grades; 1% Grade≥3) and rash (21% all grades; 1% Grade≥3). The stomatitis cases were responsive to oral dexamethasone rinses, and rash was generally mild. No DLTs were observed at the 6-mg or 9-mg dose levels with GDC-0077 as single agent or in combination with letrozole, or with palbociclib and letrozole in Study GO39374; however, DLTs of Grade 4 hyperglycemia and Grade 3 fatigue (1 patient each) were reported at the 12-mg dose level with GDC-0077 as a single agent. As of the current clinical data cutoff (20 March 2020), 4 patients (3%; N=157) had discontinued study treatment due to an adverse event (Arm B: related Grade 3 hyperglycemia; Arm F: related Grade 2 panniculitis; Arm B: unrelated Grade 3 cerebrovascular disorder; Arm D: unrelated unexplained death).

Refer to the GDC-0077 Investigator's Brochure for details on nonclinical and clinical studies.

1.4 BACKGROUND ON PALBOCICLIB

Palbociclib is an inhibitor of Cyclin Dependent Kinase 4 (CDK4) and CDK6 and is approved in combination with the aromatase inhibitor letrozole for the initial treatment of postmenopausal women or men (U.S.) with advanced or metastatic HR-positive, HER2-negative breast cancer. Palbociclib is also approved in combination with fulvestrant for the treatment of women or men (U.S.) with advanced or metastatic HR-positive, HER2-negative breast cancer that has progressed after endocrine therapy. The approval in combination with fulvestrant was based on the Phase III PALOMA-3 study, which showed that in women with HR-positive, HER2-negative advanced or metastatic breast cancer who had disease progression following endocrine therapy treatment with the combination of palbociclib and fulvestrant demonstrated a median PFS of 9.2 months (95% *CI:* 7.5 to not estimable [NE]) versus 3.8 months (95% CI: 3.5 to 5.5) for those treated with placebo and fulvestrant (hazard ratio: 0.42; 95% CI: 0.32 to 0.56; p <0.001) (Turner et al. 2015). Updated PFS analysis data from the PALOMA-3 study demonstrated a median PFS of 11.2 months in the palbociclib arm versus 4.6 months in the placebo arm (hazard ratio: 0.497) (Cristofanilli et al. 2018).

As reported in the palbociclib Summary of Product Characteristics (SmPC), the most common adverse events (≥10%) associated with the use of palbociclib in combination

with fulvestrant include neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, diarrhea, thrombocytopenia, vomiting, alopecia, rash, decreased appetite, and pyrexia.

1.4.1 Clinical Pharmacokinetics of Palbociclib

The mean maximum concentration observed (C_{max}) of palbociclib is generally observed between 6 to 12 hours (time to reach maximum concentration) following oral administration. The mean absolute bioavailability of palbociclib after an oral 125-mg dose is 46%. In the dosing range of 25 to 225 mg, the area under the concentration-time curve (AUC) and C_{max} increased proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. The geometric mean apparent oral clearance of palbociclib was 63.1 L/hr (29% $coefficient\ of\ variation$), and the mean ($\pm$standard deviation) plasma elimination half-life was 29 ($\pm$5) hours in patients with advanced breast cancer.

Palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased palbociclib exposure in this small subset of the population, but it did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Therefore, food intake reduced the inter-patient variability of palbociclib exposure, which supports administration of palbociclib with food.

In vitro and in vivo studies indicated that palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125-mg dose of [^{14}C]palbociclib to humans, the primary metabolic pathways for palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma (23%). The major circulating metabolite was a glucuronide conjugate of palbociclib, although it only represented 1.5% of the administered dose in the excreta. Palbociclib was extensively metabolized, with unchanged drug accounting for 2.3% and 6.9% of radioactivity in feces and urine, respectively. In feces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 26% of the administered dose. In vitro studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant SULT enzymes indicated that cytochrome P450 (CYP) 3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

For more information, refer to the local prescribing information for palbociclib (i.e., package insert or SmPC).

Preliminary palbociclib PK data from 23 female patients with HR-positive, HER2-negative breast cancer were evaluated in Study GO39374 when administered together with GDC-0077 and letrozole and compared with the palbociclib FDA New Drug Application clinical pharmacology review. These data indicate no effect of GDC-0077 on the pharmacokinetics of palbociclib and further indicate a low risk of GDC-0077 as a

perpetrator of CYP3A4-based drug–drug interaction (DDI). In addition, the combination of palbociclib and letrozole had no effect on the dose-normalized exposure of GDC-0077, suggesting that palbociclib will not alter GDC-0077 exposure.

1.5 BACKGROUND ON FULVESTRANT

Fulvestrant is an ER antagonist approved for the treatment of postmenopausal women with advanced HR-positive, HER2-negative breast cancer with or without prior anti-estrogen therapy. Fulvestrant is also approved in combination with the CDK4/6 inhibitor palbociclib for the treatment of advanced or metastatic HR-positive, HER2-negative breast cancer that has progressed after endocrine therapy.

Fulvestrant binds to the ER, disrupting the signaling pathway, which leads to ER degradation. The recommended dosage of fulvestrant is 500 mg given by intramuscular (IM) injection on Days 1, 15, and 29 of the first month, and then monthly thereafter. This dosage of fulvestrant was confirmed in a randomized clinical study of 250 mg versus 500 mg IM on a monthly basis (Di Leo et al. 2010). Fulvestrant 500 mg given on a monthly basis provided superior clinical benefit compared with a 250-mg dose (PFS hazard ratio: 0.80; 95% CI: 0.68 to 0.94; p=0.006), but the 500-mg dose was accompanied by a higher rate of injection-site reactions (Di Leo et al. 2010). This dose of fulvestrant has also shown a trend toward improvement in overall survival (OS) compared with the 250-mg fulvestrant dose (median duration of OS 25.1 months vs. 22.8 months; hazard ratio=0.84 [95% CI: 0.69 to 1.03; p=0.091]). The lower dose of fulvestrant (250 mg) is recommended in patients who have liver dysfunction (Child-Pugh Class B disease).

The Phase III FALCON study investigated whether fulvestrant could improve PFS compared with anastrozole in postmenopausal patients with HR-positive locally advanced or metastatic breast cancer who had not received previous endocrine therapy (Robertson et al. 2016). The median PFS was 16.6 months in the fulvestrant group versus 13.8 months in the anastrozole group (hazard ratio: 0.797, p=0.0486).

As reported in the fulvestrant SmPC, common adverse events associated with the use of fulvestrant include hypersensitivity reactions, hot flushes, nausea, elevated hepatic enzymes (ALT, AST, *alkaline phosphatase* [ALP]), rash, joint and musculoskeletal pain, asthenia, injection-site reactions, urinary tract infections, reduced platelet count, anorexia, headache, venous thromboembolism, vomiting, diarrhea, elevated bilirubin, back pain, vaginal hemorrhage, peripheral neuropathy, and sciatica. In randomized studies that compared fulvestrant with anastrozole, similar rates of common adverse events were reported, with the exception of injection-site pain.

1.5.1 Clinical Pharmacokinetics of Fulvestrant

At the 500-mg monthly dosing regimen, the geometric mean (%CV) C_{max} and AUC of fulvestrant at steady state were 28.0 ng/mL (27.9%) and 13,100 ng • hr/mL (23.4%), respectively. Following a single IM injection of fulvestrant 250 mg, the apparent

clearance (mean ± standard deviation) of fulvestrant was 690 ± 226 mL/min with an apparent half-life of approximately 40 days. The ^{14}C-labeled studies with fulvestrant indicate that fulvestrant is rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Less than 1% of fulvestrant was excreted unchanged in the urine (Faslodex® U.S. Package Insert [USPI]).

Fulvestrant has no known drug interactions. It does not significantly inhibit or induce any of the major CYP isoenzymes in vitro. Although it is partially metabolized by CYP3A4, co-administration of fulvestrant with either rifampicin (a potent CYP3A4 inducer) or ketoconazole (a potent CYP3A4 inhibitor) had no effect on its pharmacokinetics (Faslodex USPI).

Preliminary fulvestrant pharmacokinetic (PK) data from 16 female patients with HR-positive, HER2-negative breast cancer were evaluated in Study GO39374. Results suggest that the minimum concentration observed after several months of dosing is comparable to historical data suggesting no DDI with fulvestrant as a victim and GDC-0077 as a perpetrator (Faslodex USPI). Furthermore, exposure of GDC-0077 in the presence of fulvestrant is similar to GDC-0077 single-agent exposure and suggests no DDI interaction with GDC-0077 as a victim.

For more information, refer to the local prescribing information for fulvestrant (i.e., package insert or SmPC).

1.6 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

HR-positive, HER2-negative breast cancer remains a disease with significant unmet need: HR-positive tumors represent the most common form of breast cancer, yet despite adjuvant endocrine therapy, a significant proportion of patients (~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 HR-positive disease.

There are multiple mechanisms of resistance to hormonal therapies in patients with HR-positive metastatic breast cancer: estrogen-independent tumor growth; loss of ER expression; or activation of intracellular signaling pathways, including *mitogen-activated protein kinase* and PI3K (Acconcia et al. 2005; Björnström and Sjöberg 2005; Gutierrez et al. 2005; Johnston 2009; Osborne and Schiff 2011).

The addition of targeted therapies (such as PI3K/mTOR inhibitors and CDK4/6 inhibitors) to endocrine therapy may overcome mechanisms of resistance to endocrine therapies, leading to significant clinical improvements in PFS. Mechanisms of resistance to targeted therapies, such as everolimus and palbociclib, remain poorly understood but are likely multifactorial, including signaling pathway reactivation and alterations in cell-cycle components (Rb1 loss or cyclin E amplification).

The scientific rationale for combining PI3K pathway inhibition with endocrine therapy is supported by nonclinical and clinical data. Activation of the PI3K pathway (via *PIK3CA* mutations, PTEN expression loss, or HER2 overexpression) has been demonstrated to promote resistance to anti-estrogen therapy and hormonal independence in ER-positive breast cancer models (Shou et al. 2004; Miller et al. 2009, 2010). Proteomic and transcriptional profiling of human HR-positive tumors suggest that increased PI3K signaling is associated with lower ER levels, which has been correlated with resistance to endocrine therapy (Creighton et al. 2010; Miller et al. 2010). Inhibition of the PI3K/mTOR pathway in nonclinical models has been shown to upregulate ER/progesterone receptor expression (Creighton et al. 2010) and enhance the anti-tumor effect of letrozole (Boulay et al. 2005). Retrospective analyses of tumor samples from HR-positive patients who are treated with tamoxifen lend support to the nonclinical observations linking the PI3K pathway to endocrine resistance; patients with an activated PI3K pathway have been found to have decreased OS (Kirkegaard et al. 2005) and shorter relapse-free survival (Shoman et al. 2005).

In the clinical setting, data from Phase II and III studies suggest that the combined inhibition of the PI3K/mTOR and estrogen-signaling pathways provides superior benefit when compared with single-agent endocrine therapies. The addition of everolimus to tamoxifen in a Phase II study of patients with ER-positive breast cancer who received prior treatment with an aromatase inhibitor significantly improved CBR, time to progression, and OS compared with single-agent tamoxifen (Bachelot et al. 2012). Data from the Phase III BOLERO-2 study demonstrated that the addition of everolimus to exemestane more than doubled PFS compared with single-agent exemestane in patients with ER-positive, HER2-negative metastatic breast cancer whose disease was refractory to prior treatment with letrozole or anastrozole (Baselga et al. 2012).

Recent data have shown that the presence of *PIK3CA* mutations in breast cancers may confer a worse prognosis (Caldas, AACR, 2016). *PIK3CA* mutations occur in approximately 40% of HR-positive, HER2-negative breast cancers (Saal et al. 2005; Stemke-Hale et al. 2008), and inhibition of PI3K has been clinically validated in HR-positive, HER2-negative metastatic breast cancer (André et al. 2019).

Alpelisib is a selective inhibitor of the PI3Kα isoform. Data from Phase I and Ib studies with alpelisib as a single agent and in combination with fulvestrant have demonstrated anti-tumor activity and a tolerable adverse event profile (Janku et al. 2014; Juric et al. 2014). Recent data from the Phase Ib study of alpelisib in combination with letrozole provide further support for combining endocrine therapy and PI3K inhibition. In ER-positive, HER2-negative metastatic breast cancer, confirmed PRs occurred in 25% of patients with *PIK3CA*-mutant and 10% of patients with WT tumors; CBR with the combination was greater in patients with *PIK3CA*-mutant compared with WT tumors (44% vs. 20%). The most common adverse events attributed to the study treatment included hyperglycemia, nausea, fatigue, diarrhea, and rash (Mayer et al. 2019). On the basis of a subsequent Phase III study (SOLAR-1; André et al. 2019), alpelisib has

received approval from the U.S. FDA, in combination with fulvestrant, for the treatment of patients with HR-positive, HER2-negative, *PIK3CA*-mutated advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. In the cohort of 341 patients with *PIK3CA*-mutated cancer, PFS at a median follow-up of 20 months was 11.0 months (95% CI: 7.5 to 14.5 months) in the alpelisib plus fulvestrant group compared with 5.7 months (95% CI: 3.7 to 7.4 months) in the placebo plus fulvestrant group (hazard ratio = 0.65; 95% CI: 0.50 to 0.85; $p < 0.001$). Among all patients in SOLAR-1, the most frequent Grade 3 or 4 adverse events were hyperglycemia (36.6% in the alpelisib plus fulvestrant group vs. 0.7% in the placebo plus fulvestrant group) and rash (9.9% vs. 0.3%). Grade 3 diarrhea occurred in 6.7% versus 0.3% of patients. Twenty-five percent of patients treated with alpelisib permanently discontinued treatment due to adverse events versus 4.2% of patients in the placebo arm.

Thus, combined inhibition of the PI3K/mTOR and estrogen-signaling pathways offers an effective therapeutic approach in patients with HR-positive, HER2-negative metastatic breast cancer.

The scientific rationale for combining a PI3K pathway inhibitor with CDK4/6 inhibitor therapy is supported by nonclinical data, and these combinations together with endocrine therapy are being evaluated in clinical trials. A combinatorial drug screen of *PIK3CA*-mutant cancers found that combined CDK4/6-PI3K inhibition synergistically reduced tumor cell viability (Vora et al. 2014). PI3K inhibitor treatment of palbociclib-arrested cells results in cell death, although the combination of CDK4/6-PI3K inhibition was not able to re-sensitize cancer cell lines with acquired resistance to CDK4/6 inhibition. Importantly, in vivo data demonstrate that the combination of CDK4/6 and PI3K inhibition can prevent or delay the time to CDK4/6 inhibitor resistance (Herrera-Abreu et al. 2016).

Currently, aromatase inhibitors and tamoxifen are approved for use in the adjuvant and locally advanced or metastatic setting whereas fulvestrant is approved for use in the locally advanced or metastatic setting only. Given its distinct mechanism of action, fulvestrant, in combination with palbociclib, represents an appropriate treatment option for patients who experience disease progression during or shortly after completing adjuvant endocrine therapy. This combination is supported by data from the PALOMA-3 clinical trial (Cristofanilli et al. 2016).

Patients whose disease progressed during or within 12 months of completion of adjuvant endocrine therapy or whose disease progressed on or within 1 month of prior endocrine therapy for advanced or metastatic disease enrolled in PALOMA-3. Patients with measurable or bone-only disease (limited to lytic or mixed lytic/blastic) were also eligible. Overall, patients who had received neoadjuvant or adjuvant therapy only but no prior systemic therapy for metastatic disease achieved a median PFS of 9.5 months (95% CI: 7.4 months to NE) with palbociclib and fulvestrant, comparable to patients who

had received at least one prior systemic therapy for metastatic breast cancer and achieved a median PFS of 9.9 months (95% CI: 9.2 to 11.2 months). While the relative benefit of adding CDK4/6 inhibition to endocrine therapy is independent of *PIK3CA* mutation status, median PFS was shorter in patients with *PIK3CA* mutations detectable in circulating tumor DNA (ctDNA) versus patients with no *PIK3CA* mutations in ctDNA in the PALOMA-3 study regardless of treatment arm (5.8 months [95% CI: 5.3 to 9.5 months] vs. 9.2 months [95% CI: 7.5 to 10.8 months]) (Cristofanilli et al. 2016). In addition, shorter survival has been observed in patients with *PIK3CA* mutations detectable in ctDNA (Turner et al. 2018).

Improved treatment options for HR-positive, HER2-negative breast cancer may ultimately decrease or eliminate the risk of late recurrences after adjuvant therapy, provide more tolerable effective treatment options, and ultimately achieve a cure for patients with advanced or metastatic disease. The anticipated or potential safety issues associated with administration of GDC-0077 as a single agent or in combination with palbociclib and/or endocrine therapy are expected to be clinically monitorable and manageable in patients. The measures to avoid or minimize such toxicities in this trial are described in detail in Section 5.1.

The specificity of inavolisib for the PI3Kα-isoform, together with its unique mechanism of action that leads to specific degradation of mutant p110α, should enable a clinically-effective therapeutic index as a single agent and in combination with standard-of-care endocrine and targeted therapies. On the basis of all nonclinical data available for inavolisib and clinical data from the Phase I/Ib study (GO39374) as reported in the inavolisib Investigator's Brochure, the Sponsor has assessed the benefit–risk profile of inavolisib as a single agent and in combination with standard-of-care endocrine and targeted therapies to be appropriate for initiating this Phase III clinical study.

1.6.1 COVID-19

In the setting of the coronavirus disease *2019* (COVID-19) pandemic, patients with comorbidities, including those with metastatic cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19. However, it is unclear whether or how systemic cancer therapies such as chemotherapy or targeted therapy may affect the incidence or severity of COVID-19.

Since immunosuppressant effects are a potential risk for inavolisib and myelosuppression, a possible consequence of immunosuppression may lead to an increased susceptibility to acute infections including COVID-19.

At this time, there is insufficient evidence for causal association between inavolisib and an increased risk of severe outcomes from COVID-19.

Pneumonitis is a potential risk for inavolisib and a few cases of Grade 1–2 pneumonitis have been observed upon treatment with inavolisib. There may be a potential overlap in

clinical and radiological features for inavolisib induced pneumonitis and COVID-19–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of inavolisib in combination with palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant in patients with *PIK3CA*-mutant, HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. Specific objectives and corresponding endpoints for the study are outlined below.

Throughout this protocol, "study drug" refers to any of the individual agents assigned to patients as part of this study (i.e., inavolisib, placebo, palbociclib, or fulvestrant), while "study treatment" refers to the combination of agents assigned to patients as part of this study (i.e., inavolisib plus palbociclib and fulvestrant, or placebo plus palbociclib and fulvestrant).

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant 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 inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoints:

- Objective response rate, defined as the proportion of patients with a CR and/or PR on at least two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to RECIST v1.1
- Best overall response rate (BOR), defined as the proportion of patients with a CR or PR, as determined by the investigator according to RECIST v1.1
- DOR, defined as the time from the first occurrence of a CR or PR 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
- CBR, defined as the proportion of patients with a CR, PR, and/or SD for at least 24 weeks, as determined by the investigator according to RECIST v1.1

- OS, defined as the time from randomization to death from any cause
- Time to deterioration (TTD) in pain, defined as the time from randomization to the first documentation of a ≥2-point increase from baseline on the "worst pain" item from the Brief Pain Inventory–Short Form (BPI-SF)
- TTD in Physical Function, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ-C30) Physical Function scale (items 1–5)
- TTD in Role Function, defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-C30 Role Function scale (items 6 and 7)
- TTD in global health status (GHS)/health-related quality of life (HRQoL), defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the EORTC QLQ-30 GHS/HRQoL scale (items 29 and 30)

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoints:

- Time to end of next-line treatment (proxy for time to second objective disease progression [PFS2]), defined as the time from randomization to end or discontinuation of next-line treatment, or death from any cause (whichever occurs first)
- Time to first skeletal-related event (SRE), defined as the time from randomization to the first occurrence of an SRE

  A SRE is a pathologic fracture, radiation therapy to bone, cancer-related surgery to bone, or spinal cord compression.
- Mean and mean change-from-baseline scores in all functions (Physical, Role, Cognitive, Emotional, and Social), GHS/HRQoL, and disease- or treatment-related symptom scores, as measured by the scales of the EORTC QLQ-C30 and EORTC QLQ–Breast Cancer Module 23 Questionnaire (EORTC QLQ-BR23)

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant 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

- Change from baseline in ECG parameters

The exploratory safety objective for this study is to evaluate the tolerability of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant from the patient's perspective, on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities (i.e., diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash symptoms) as assessed through use of the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument, as well as an additional item regarding the overall bother experienced due to side effects of treatment
- Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE and the additional bother item

2.3 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to characterize the pharmacokinetics of inavolisib, palbociclib, and fulvestrant, when administered in combination in this population, on the basis of the following endpoints:

- Plasma concentration of inavolisib at specified timepoints
- Plasma concentration of palbociclib at specified timepoints
- Plasma concentration of fulvestrant at specified timepoints

The exploratory PK objective is to evaluate potential relationships between the plasma exposure of inavolisib, palbociclib, and fulvestrant and efficacy and safety outcomes from this study.

The China-specific pharmacokinetic objective is to characterize the pharmacokinetics of inavolisib in all patients enrolled in China.

2.4 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study are to identify and/or evaluate biomarkers that are associated with response and disease control with the study treatments, are early surrogates of efficacy of the study treatments, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with innate or acquired resistance to the study treatments, 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 activity of the study treatments (i.e., pharmacodynamic biomarkers), 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 4.5.6) and efficacy, safety, PK, 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 inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoint:

- Health utility and visual analog score (VAS) of the European Quality of Life 5-Dimension, 5 Level (EQ-5D-5L) Questionnaire

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

Study WO41554 is a Phase III, randomized, double-blind, placebo-controlled, multicenter, global study designed to compare the efficacy, as measured by PFS, and the safety of the triplet combination of inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant in patients with *PIK3CA*-mutant, HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease.

Approximately 320 patients will be enrolled at approximately 200 global investigative sites.

Patients will be randomized to one of the following treatment arms in a 1:1 ratio (randomization will be stratified [see Section 4.2.1]):

Inavolisib plus palbociclib and fulvestrant

- Inavolisib: 9-mg tablet taken PO QD on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1
- Palbociclib: 125-mg capsule or tablet taken PO QD on Days 1–21 of each 28-day cycle, beginning on Day 1 of Cycle 1
- Fulvestrant: 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks

Placebo plus palbociclib and fulvestrant

- Placebo: tablet taken PO QD on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1
- Palbociclib: 125-mg capsule or tablet taken PO QD on Days 1–21 of each 28-day cycle, beginning on Day 1 of Cycle 1
- Fulvestrant: 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks

The study consists of a screening period of up to 28 days, a treatment period, a post-treatment follow-up period (which includes a “30-day safety follow-up” for all patients and, when applicable, a “post-treatment hyperglycemia follow-up,” and/or a “post-treatment tumor assessment follow-up with PRO collection”), and a survival follow-up period, as shown in Figure 1 and Appendix 1.

Patients may be prescreened for *PIK3CA*-mutation status through central testing of ctDNA by participating in a separate prescreening consent. Patients may be re-screened only in cases of study-required assessments falling out of the screening window; all other screen failures are exclusionary.

Study treatment may continue until unequivocal disease progression as determined by the investigator, unacceptable toxicity, patient withdrawal of consent, or study termination.

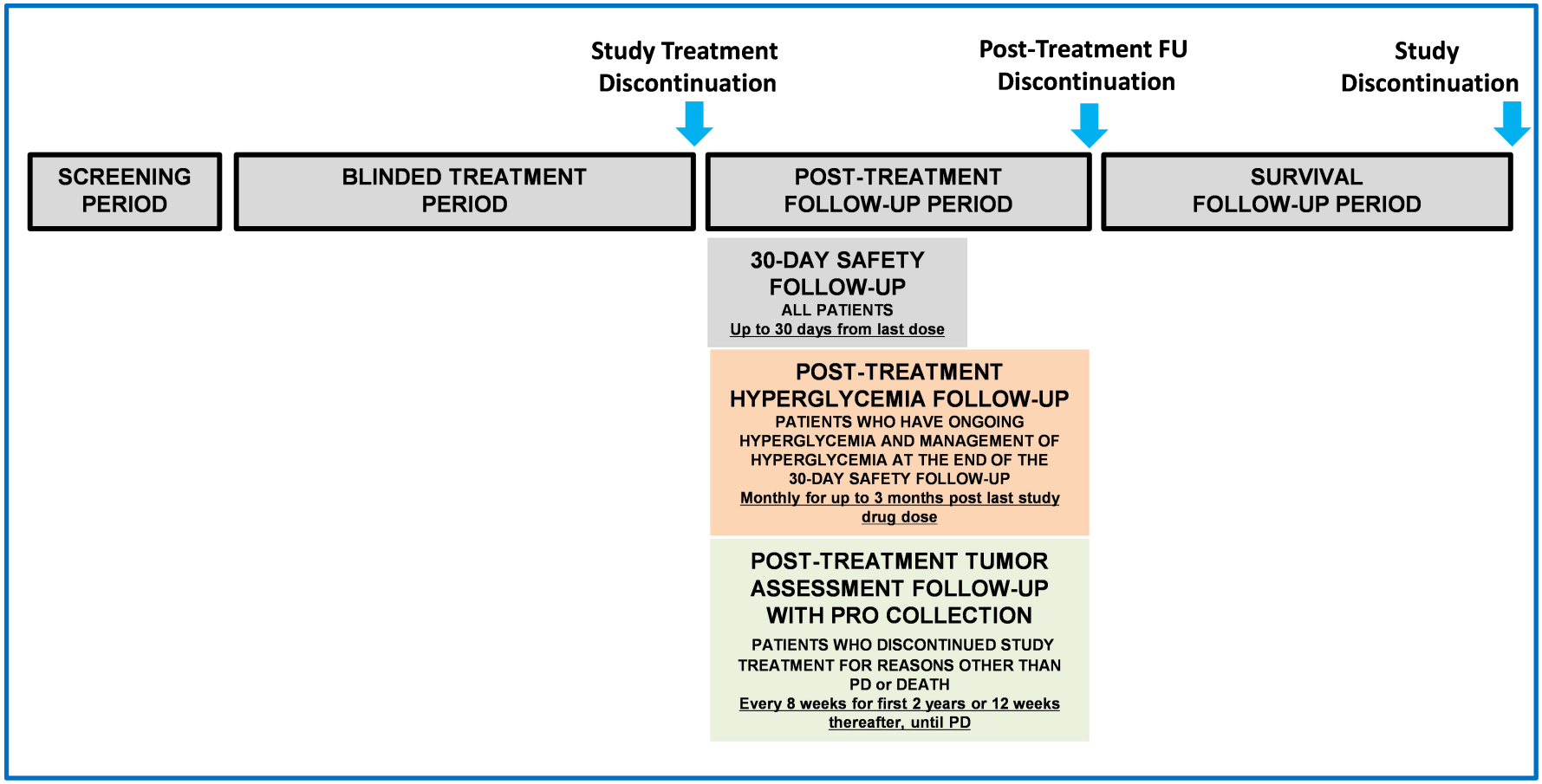
Following study treatment discontinuation, patients will be followed for safety for 30 days after final study treatment (30-day safety follow-up, including a 30-day follow-up visit), or until the initiation of another anti-cancer therapy, whichever occurs first.

Patients on anti-hyperglycemic agents for the treatment of hyperglycemia during the study treatment period and those patients with events of hyperglycemia ongoing at the end of the 30-day safety follow-up, will undergo additional safety follow-up assessments (“post-treatment hyperglycemia follow-up”) monthly until resolution of their fasting glucose to baseline levels, complete down-titration of their anti-hyperglycemic medications, or up to approximately 3 months after the final dose of study treatment, even if the patient initiates another anti-cancer therapy subsequent to study treatment discontinuation.

In addition, patients who discontinue active study treatment for reasons other than progression of disease or death will continue to have tumor assessments performed every 8 weeks (±7 days) for the first 2 years from randomization and every 12 weeks (±7 days) thereafter, and complete PRO assessments at those timepoints (“post-treatment tumor assessment follow-up with PRO collection”), until documented disease progression or the initiation of another anti-cancer therapy, whichever occurs first.

All patients will subsequently move onto the survival follow-up period until death, patient withdrawal of consent, loss to follow-up, or study termination.

Figure 1 Schematic of Study Periods



FU = follow up; PD = progressive disease; PRO = patient-reported outcome.

Study patients must have measurable disease (per RECIST v1.1; see Appendix 9). Patients with evaluable (non-measurable) bone-only disease are not eligible; disease that is limited to bone but that has lytic or mixed lytic/blastic lesions and at least one measurable soft-tissue component (per RECIST v1.1) may be eligible. Detailed eligibility information is listed in the inclusion and exclusion criteria in Sections 4.1.1 and 4.1.2. Locally advanced disease must not be amenable to resection or other local therapy with curative intent.

Patients may enroll based on eligible *PIK3CA* mutation results from testing performed by a central investigational testing site or a site local test. Local testing of blood or tumor tissue must be performed using a Sponsor-approved polymerase chain reaction (PCR)-based or next-generation sequencing (NGS) assay at a Clinical Laboratory Improvement Amendments (CLIA)- or equivalently-certified laboratory. Patients without available local test results for *PIK3CA* mutation status must submit a blood sample to determine whether an eligible *PIK3CA* mutation is present. Samples will be evaluated by the NGS-based FoundationOne® Liquid CDx (F1LCDx) assay, unless not implemented in specific localities. In this case, samples will be submitted to an alternative, Sponsor-designated central testing laboratory. Regardless of the testing strategy to determine a patient's tumor *PIK3CA* mutation status, all patients must provide both blood and tumor tissue for evaluation by a central investigational testing site. Demographic data will be collected on all patients who undergo screening, including those who screen fail.

Patients will be closely monitored for adverse events throughout the study treatment, and for 30 days after the final dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Adverse events will be graded according to NCI CTCAE v5.0. Patients who, at the 30-day safety follow-up visit, are still on anti-hyperglycemic agents for the treatment of hyperglycemia during the study treatment, and those patients with events of hyperglycemia ongoing at the 30-day safety follow-up visit, will go on to the post-treatment hyperglycemia follow-up (as defined above).

Tumor assessments will be performed to assess for response every 8 weeks (±7 days) during the first 2 years of study treatment and every 12 weeks (±7 days) thereafter. Patients who discontinue active study treatment for any reason other than unequivocal disease progression or death will follow the same tumor assessment schedule during the "post-treatment tumor assessment follow-up with PRO collection" period.

After study treatment discontinuation, all patients will be followed for survival and all subsequent anti-cancer therapies. These data will be collected via telephone calls and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

To evaluate the PK properties of inavolisib, palbociclib, and fulvestrant administered in this triplet combination, blood samples will be taken at various timepoints before and after dosing (Appendix 2).

Patient reported outcome instruments will be completed by patients to evaluate the treatment impact from the patient's perspective as specified in the schedule of activities (Appendix 1). The EORTC QLQ-C30 will assess disease and treatment-related symptoms often experienced by patients with locally advanced or metastatic cancer including fatigue, pain, depression/anxiety, and any limitations in function. The EORTC QLQ-BR23 will provide additional assessment on some treatment-related symptoms and symptoms that may occur with advanced disease. The “worst pain” item from the BPI-SF will be used to evaluate an increase in pain severity. Additionally, the PRO-CTCAE will be used to assess the impact of treatment-related symptoms, with the goal being to demonstrate benefit of treatment without adverse impact on patients’ HRQoL. The EQ-5D-5L will be used to assess health status.

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

Figure 2 Study Schema

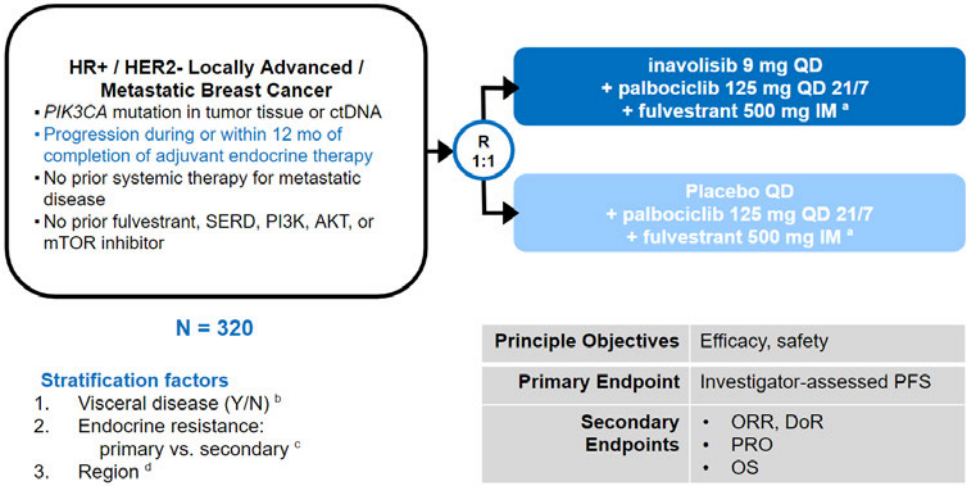


Figure 2: Study Schema; Section 3.1.1

AKT = protein kinase B; ctDNA = circulating tumor DNA; DOR = duration of response; HER2 − = HER2-negative; HR + = hormone-receptor positive; IM = intramuscular; mTOR = mammalian target of rapamycin; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI3K = phosphatidylinositol 3-kinase; PRO = patient-reported outcome; QD = once daily; SERD = selective estrogen-receptor degrader.

[a] Fulvestrant is administered on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks.

[b] "Visceral" (Yes/No) refers to lung, liver, brain, pleural, and peritoneal involvement.

[c] Primary endocrine therapy resistance is defined as relapse while on the first 2 years of adjuvant endocrine therapy. Secondary endocrine therapy resistance is defined as relapse while on adjuvant endocrine therapy but after the first 2 years or relapse within 12 months of completing adjuvant endocrine therapy (4th ESO–European Society for Medical Oncology [ESMO] International Consensus Guidelines for Advanced Breast Cancer [ABC4], Cardoso et al. 2018).

[d] Region is stratified by site location: i) North America/Western Europe, ii) Asia/Pacific, iii) Other.

3.1.2 Independent Data Monitoring Committee

An external independent Data Monitoring Committee (iDMC) will be formed to evaluate safety data from the first patient randomized until the time of the primary analysis of PFS and to conduct the interim analysis (see Section 6.9). The iDMC will monitor accumulating patient safety data approximately every 4 months during the course of the study. The iDMC will include qualified personnel, all independent of the Sponsor, who are committed to preservation of the trial integrity and reaching valid conclusions as described in the iDMC guidance. The primary responsibilities of the iDMC will be to thoroughly review the available cumulative safety data and to make recommendations regarding modification of the conduct of study, enrollment hold, performance of additional interim safety analyses, changes to the inclusion/exclusion criteria or safety evaluation, or termination of the study if there is evidence of undue risk to the study participants.

The analyses will be conducted by an independent Data Coordinating Center and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

3.1.3 Blinded Independent Central Imaging Review

To facilitate a blinded independent central review (BICR) for PFS, all radiological data (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan) and photographs for skin lesions obtained at baseline, during the treatment period, at the time of disease progression, and at the time of study treatment discontinuation (if not the same as disease progression) should be sent to a central imaging vendor (contracted by the Sponsor) within 2 weeks of imaging to enable retrospective BICR. Additional details about tumor assessment collections and readings will be outlined in a separate charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Inavolisib, Palbociclib, and Fulvestrant Doses and Schedules

This study will evaluate inavolisib (9-mg PO QD) or placebo equivalent in combination with palbociclib (125-mg capsule or tablet dose taken PO QD on Days 1–21 of each 28-day cycle, beginning on Day 1 of Cycle 1) and fulvestrant (500-mg administered by

IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks).

The palbociclib dose of 125-mg PO QD on Days 1–21 of each 28-day cycle and the fulvestrant dose of 500-mg IM on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks, represent the dosage approved for the treatment of adult patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with disease progression following endocrine therapy.

In the Phase I study GO39374, median dose intensity for GDC-0077 (inavolisib) was similar as a single agent and in combination with letrozole, with fulvestrant, or with palbociclib and letrozole (range: 97%–99%). No DLTs were observed at the 6-mg or 9-mg dose levels with GDC-0077 as single agent or in combination with letrozole, or with palbociclib and letrozole. Based on the available data from Study GO39374, the 9-mg PO QD GDC-0077 (inavolisib) dose, in combination with the full-approved doses of palbociclib and fulvestrant, was selected as the recommended Phase II/III dose and schedule to maximize efficacy while ensuring tolerability. Please refer to the Inavolisib Investigator's Brochure for additional information.

3.3.2 Rationale for Patient Population

The population described by the eligibility criteria reflects patients for whom the combination of palbociclib and fulvestrant represents an appropriate standard-of-care therapy. The requirement for disease progression during or within 12 months of completion of adjuvant endocrine therapy identifies patients who have become resistant to endocrine therapy and would be an appropriate population for treatment with the combination of palbociclib and fulvestrant. Patients with *PIK3CA*-mutant, HR-positive, HER2-negative locally advanced or metastatic breast cancer who have shown evidence of endocrine resistance are expected to have clinical benefit from the addition of a PI3K inhibitor. The requirement for patients to have tumors with confirmed mutations in *PIK3CA* is based on the mechanism of action for inavolisib as a selective $p110\alpha$ inhibitor and mutant $p110\alpha$ degrader, and that inhibition of PI3Kα has been clinically validated in *PIK3CA*-mutant, HR-positive, HER2-negative metastatic breast cancer (André et al. 2019). The inclusion criterion of Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–1 (Appendix 9) has been selected to test a more homogeneous patient population and to mitigate potential additional toxicities incurred by the addition of inavolisib to palbociclib and fulvestrant treatment.

3.3.3 Rationale for Exclusion of Diabetic Patients

Patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring systemic treatment are excluded from this study, and enrollment is further restricted for patients at risk for diabetes based on fasting glucose levels (<126 mg/dL [<7.0 mmol/L]) and glycosylated hemoglobin (HbA1c) (<6.0% [<42 mmol/mol]).

As inhibition of the PI3K/AKT/mTOR pathway disrupts the insulin-signaling pathway, glucose uptake and glycogen synthesis are frequently disrupted with treatments that suppress key pathway nodes, including PI3Kα (Saltiel and Kahm 2001). Additionally, PI3Kα has a major role in maintaining glucose homeostasis (Engelman et al. 2006; Foukas et al. 2006; Luo et al. 2006). As a result, inhibition of the PI3K/AKT/mTOR pathway can lead to the loss of glucose regulation, manifested in patients as hyperglycemia. A meta-analysis of the incidence and severity of hyperglycemia in clinical trials targeting the PI3K/AKT/mTOR pathway (Geuna et al. 2015) illustrated the prevalence of severe (Grade $\geq$ 3) hyperglycemia with inhibitors targeting mTOR, AKT, or PI3K. Clinical experience with PI3Kα-inhibition has shown that hyperglycemia is generally early onset (within the first 1–2 weeks of PI3Kα-inhibitor treatment) and is manageable with oral anti-hyperglycemic medications (e.g., metformin), sometimes accompanied with brief treatment interruption. What is not well understood is the benefit–risk for patients predisposed to hyperglycemia prior to initiation of PI3K-inhibitor therapy, including patients with Type 1 or 2 diabetes. To date, the Sponsor has collected limited clinical data on the treatment of *patients with diabetes* with inavolisib, and thus such patients will be excluded from the Phase III study until more clinical information has been collected and analyzed in contemporaneous studies.

3.3.4 Rationale for Control Group

Treatment for HR-positive, HER2-negative, locally advanced or metastatic breast cancer usually consists of multiple rounds of endocrine therapy alone or in combination with CDK4/6 or mTOR inhibition—if these agents have not been utilized before—followed by cytotoxic chemotherapy when all endocrine therapy options have been exhausted or when symptomatic or rapid disease progression warrants use of cytotoxic chemotherapy. Fulvestrant has been approved in the United States and European Union for the treatment of HR-positive advanced or metastatic breast cancer in postmenopausal women with disease progression following prior anti-estrogen therapy (Howell et al. 2002; Osborne et al. 2002; Di Leo et al. 2010). Fulvestrant is an ER antagonist and an effective treatment for postmenopausal patients with HR-positive breast cancer that is relatively well tolerated. The combination of an ER antagonist such as fulvestrant and a CDK4/6 inhibitor such as palbociclib has become standard-of-care in this target patient population, and thus is appropriate for the placebo-controlled arm of this study.

The anti-tumor activity of combined inhibition of cell-cycle checkpoint inhibition (palbociclib) and ER signaling (fulvestrant) may be further synergized by the addition of a PI3K/AKT/mTOR pathway inhibitor in patients whose tumors exhibit dysregulation of this pathway. Nonclinical data supported by Phase I/Ib (Study GO39374) clinical data indicate that the anti-PI3K activity of inavolisib in combination with palbociclib and fulvestrant confers additional tumor growth inhibition and efficacy beyond the combination of palbociclib and fulvestrant. Therefore, it is expected that the triplet

combination of inavolisib plus palbociclib and fulvestrant is likely to confer improved efficacy in the proposed patient population.

3.3.5 Rationale for Double-Blind Design

A double-blind, placebo-controlled design was chosen for this study to reduce the potential for bias by patients and investigators that would be related to knowledge of the treatment assignment. For patients, the design is anticipated to minimize dropout and increase compliance; for investigators, the design facilitates objectivity in outcome assessments. This design is especially important when investigator-assessed PFS is the primary endpoint.

3.3.6 Rationale for Biomarker Assessments

HR-positive, HER2-negative breast cancer is a heterogeneous disease, and *PIK3CA* mutation status has been shown to vary among patients (Cancer Genome Atlas, 2012; Curtis et al. 2012). In addition to *PIK3CA* mutation status, samples will be assessed for additional biomarkers in an effort to identify factors that may correlate with the safety and efficacy of treatment with inavolisib and/or palbociclib and fulvestrant.

3.3.6.1 Rationale for Using Circulating Tumor DNA for Examining *PIK3CA* Mutation Status

Mutations in *PIK3CA* occur at a frequency of approximately 40% in HR-positive, HER2-negative breast cancer and have been shown to be associated with response to PI3K inhibitors (O'Brien et al. 2010; Schleifman et al. 2014; André et al. 2019). There is increasing evidence that ctDNA obtained from blood specimens of patients with cancer is representative of the DNA and mutational status of tumor cells (Diehl et al. 2008; Maheswaran et al. 2008). Currently available assays (e.g., droplet-digital PCR, NGS) can detect the major *PIK3CA* mutations (and other cancer-related gene alterations) in plasma, and results from this analysis correlate with mutation results from tumor tissue specimens (Clark et al., 2018). Previous studies suggest that the acquisition of *PIK3CA* mutations is an early event in breast cancer (Miron et al. 2010) and that detection of *PIK3CA* mutations between plasma-derived ctDNA and tumor tissue specimens is largely concordant (Kodahl et al. 2018). For these reasons, the use of ctDNA to identify patients with *PIK3CA*-mutant tumors through NGS is an appropriate minimally invasive method for determining patients' biomarker eligibility for this study. NGS may also be performed on blood and/or plasma samples collected at various times during study treatment and at the time of disease progression to understand potential changes in *PIK3CA* mutation frequency and investigate potential mechanisms of response and resistance to the study treatment.

3.3.6.2 Rationale for the Collection of Tissue Samples

To better understand the role of alterations detected in tumor tissue and to support future diagnostic development, a fresh or archival tumor tissue sample from metastatic disease or from a primary breast tumor collected prior to the start of study treatment will

be profiled for mutations in hundreds of cancer-related genes, including *PIK3CA*, using NGS.

This approach offers the opportunity to perform molecular subtyping that may inform breast cancer biology and response to inavolisib or other PI3K/AKT/mTOR pathway inhibitors, to endocrine therapy, or to CDK4/6 inhibition. Furthermore, sequencing of cancer-related genes may identify de novo mechanisms of resistance to the study treatment.

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.

Next-generation sequencing analysis may also be performed on tumor tissue samples collected during study treatment or at the time of disease progression from patients who provide optional consent.

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

Investigator-assessed PFS is regarded as a clinically relevant measure of treatment benefit and an approvable endpoint in the setting of HR-positive, HER2-negative locally advanced or metastatic breast cancer. For example, in the PALOMA-3 study, investigator-assessed median PFS for palbociclib plus fulvestrant and placebo plus fulvestrant arms 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. The associated PFS hazard ratio was 0.46 (95% CI: 0.36 to 0.59) (Cristofanilli et al. 2016). These results led to the approval of the combination of palbociclib and fulvestrant.

The randomized, double-blind, placebo-controlled study design is intended to limit the risk of investigator bias in the assessment of treatment impact. In addition, a BICR of tumor assessment data will be performed to support the primary endpoint of investigator-assessed PFS.

3.3.8 Rationale for Clinical Outcome Assessments

As metastatic breast cancer is not curable with currently approved and available therapies, the primary focus for patients is on living as long as possible and delaying the progression of cancer while maintaining their quality of life and the ability to carry out daily activities (Cardoso et al. 2012). Research indicates that a higher proportion of *patients who are HR-positive* 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. Examining and measuring patients' disease-related pain and interference with functioning is important to capture. 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 EORTC QLQ-C30 will be administered to patients to assess disease and treatment-related symptoms, functioning, and GHS/HRQoL (see Section 4.5.9 and Appendix 4). The EORTC QLQ-BR23 will provide an additional assessment of some treatment-related symptoms and symptoms that may occur with advanced disease (Section 4.5.9 and Appendix 5). The "worst pain" item from the BPI-SF (Section 4.5.9 and Appendix 6) will be used to gain further insight into increase in pain severity. In order to evaluate the tolerability of inavolisib plus palbociclib and fulvestrant, 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, as well as an additional item regarding bother due to side effects of treatment (see Section 4.5.9 and Appendix 7). These symptoms were identified as being salient to patients' experience with inavolisib, palbociclib, and fulvestrant on the basis of preliminary safety data for inavolisib and published safety data for palbociclib and fulvestrant (see Section 1.4 and 1.5). The EQ-5D-5L (see Section 4.5.9 and Appendix 8) will also be collected and utilized to derive health states for use in economic models and $thus$ the results will not be reported in the Clinical Study Report.

3.3.9 Rationale for Pharmacokinetic Sample Collection

A sparse sampling strategy will be applied in this study. Samples for PK characterization of inavolisib, palbociclib, and fulvestrant will be collected as outlined in Appendix 2. Samples will be collected on Day 8 of Cycle 1 and Day 15 of both Cycle 1 and Cycle 2 to determine steady-state pharmacokinetics for inavolisib and palbociclib. The sampling schedule is designed to enable estimation of inavolisib key PK parameters using population PK methodology in individual patients. In addition, the PK of inavolisib, palbociclib, and fulvestrant from this study will be compared with PK data from previous studies for each agent when administered alone to evaluate whether exposures are altered when administered in combination or in this patient population.

3.3.9.1 Rationale for Intense Pharmacokinetic Sample Collection in Chinese Patients

Intensive PK samples will be collected from approximately *30-40* patients enrolled in China in this study to characterize inavolisib PK in Chinese patients. The PK parameters of inavolisib in these patients will be compared with those in non-Chinese patients from Arm E of the Phase I study (GO39374). *The schedule of intense PK sampling in Chinese patients is provided in* Appendix 3.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately *320* patients with *PIK3CA*-mutant, HR-positive, HER2-negative locally advanced or metastatic breast cancer will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Women or men ≥ 18 years of age at time of signing Informed Consent Form
- If female, patients must meet at least one of the following definitions:

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

  – Age ≥ 60 years

  – Age < 60 years and 12 months of amenorrhea plus follicle-stimulating hormone and plasma or serum 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 to baseline)

  Premenopausal or perimenopausal (i.e., not meeting the criteria for postmenopausal) and meeting the following criterion:

  – Treatment with luteinizing hormone–releasing hormone (LHRH) agonist therapy (e.g., goserelin or leuprolide) beginning at least 2 weeks prior to Day 1 of Cycle 1 and continuing for the duration of study treatment

  If male, recommendation of treatment with LHRH agonist therapy (e.g., goserelin or leuprolide) beginning at least 2 weeks prior to Day 1 of Cycle 1 and continuing for the duration of study treatment
- Histologically or cytologically confirmed adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to surgical or radiation therapy with curative intent
- Documented ER–positive and/or progesterone receptor–positive tumor according to American Society of Clinical Oncology/College of American Pathologists

(ASCO/CAP) guidelines, defined as $\geq$1% of tumor cells stained positive based on the most recent tumor biopsy and assessed locally

- Documented HER2-negative tumor according to ASCO/CAP guidelines, defined as a HER2 immunohistochemistry (IHC) score of 0 or 1+, or an IHC score of 2+ accompanied by a negative fluorescence, chromogenic, or silver in situ hybridization test indicating the absence of *HER2* gene amplification, or a HER2/CEP17 ratio of $<$ 2.0 based on the most recent tumor biopsy and assessed locally
- Confirmation of biomarker eligibility: valid results from either central testing of blood or local testing of blood or tumor tissue documenting *PIK3CA*-mutant tumor status

  Eligible *PIK3CA* mutations are defined as follows:

H1047D/I/L/N/P/Q/R/T/Y	**G1049**A/C/D/R/S
E545A/D/G/K/L/Q/R/V	**E453**A/D/G/K/Q/V
E542A/D/G/K/Q/R/V	**K111**N/R/E
Q546E/H/K/L/P/R	**G106**A/D/R/S/V
N345D/H/I/K/S/T/Y	**G118**D
C420R	**R88**Q
M1043I/T/V	

  The central test for identification of eligible *PIK3CA* mutations is the F1LCDx assay performed at Foundation Medicine, Inc. (*FMI*). In localities where this is not available, samples will be submitted to an alternative, Sponsor-designated central testing laboratory.

  All patients are required to submit a freshly collected pre-treatment blood sample, whether patients are enrolled by local or central test results.

  Local tests of blood or tumor tissue may only be performed using a Sponsor pre-approved PCR- or NGS–based assay at a CLIA–certified or equivalent laboratory. The full laboratory report of the *PIK3CA* mutation result must be available and submitted for confirmation.

  Local test results reported from blood should be from a blood specimen representative of patient's metastatic disease state, collected after conclusion of patient's most recent anti-cancer therapy.

  Local test results reported from tumor tissue should be from the patient's metastatic disease state whenever possible.
- Consent to provide fresh (preferred) or archival tumor tissue specimen. It is preferred that the specimen be from the most recently collected and available tumor tissue, and whenever possible, from a metastatic site of disease. See the laboratory manual for specimen requirements.
- Patients must have progressed during adjuvant endocrine treatment or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen.

If a CDK4/6 inhibitor was included as part of neoadjuvant or adjuvant therapy, progression event must be > 12 months since completion of CDK4/6 inhibitor portion of neoadjuvant or adjuvant therapy.

- Measurable disease per RECIST v1.1

  Patients with evaluable bone-only disease are not eligible; disease that is limited to bone but has lytic or mixed lytic/blastic lesions and at least one measurable soft-tissue component per RECIST v1.1 may be eligible.

- Treatment with endocrine-based therapy (e.g., palbociclib and fulvestrant) is recommended at time of entry into the study, as per national or local treatment guidelines

- For women of childbearing potential: 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 at least 60 days after the final dose of study treatment. Based on local prescribing information for fulvestrant, patients may be advised to use an effective means of contraception for up to 2 years after the final dose of fulvestrant. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, 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.

  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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 98 days after the final dose of study treatment to avoid exposing the embryo. Based on local prescribing information for fulvestrant, patients may be advised to use an effective means of contraception for up to 2 years after the

final dose of fulvestrant. 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 acceptable methods of contraception.
If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

- ECOG Performance Status of 0 or 1
- Life expectancy of >6 months
- Adequate hematologic and organ function within 14 days prior to initiation of study treatment, defined by the following:
  - Absolute neutrophil count $\geq 1500/\mu L$
  - Hemoglobin ≥ 9 g/dL
  - Platelet count $\geq 100{,}000/\mu L$
  - Fasting glucose <126 mg/dL (<7.0 mmol/L) and HbA1c $<6.0\%$ (<42 mmol/mol)

    For patients with fasting glucose ≥ 100 mg/dL (≥ 5.5 mmol/L) (i.e., threshold for pre-diabetes) at baseline, recommend lifestyle changes according to American Diabetes Association guidelines; that is, dietary advice (e.g., small frequent meals, low carbohydrate content, high fiber, balanced carbohydrate intake over the course of the day, three small meals and two small snacks rather than one large meal) and exercise. Consultation with an endocrinologist or diabetologist is highly recommended.
  - Total bilirubin $\leq 1.5\times$ upper limit of normal (ULN) ($<3\times$ ULN if Gilbert's disease)
  - Serum albumin ≥ 2.5 g/dL (25 g/L)
  - AST and ALT $\leq 2.5\times$ ULN with the following exception:

    Patients with documented liver metastases: AST and ALT $\leq 5.0\times$ ULN
  - ALP $\leq 2.5\times$ ULN with the following exception:

    Patients with documented liver or bone metastases: ALP $\leq 5.0\times$ ULN
  - Creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation

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

  - INR $<1.5\times$ ULN and aPTT $<1.5\times$ ULN

    For patients requiring anticoagulation therapy with warfarin or similar agents (such as Vitamin K antagonists), a stable INR between 2 and 3 is required. If anticoagulation is required for a prosthetic heart valve, then stable INR between 2.5 and 3.5 is permitted. Consult the local prescribing information for fulvestrant.

- Ability, in the investigator's judgment, and willingness to comply with all study-related procedures, including completion of patient-reported endpoints
- For patients enrolled in China: current resident of mainland China and must be of Chinese ancestry.

4.1.2 Exclusion Criteria

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

- Metaplastic breast cancer
- Any history of leptomeningeal disease or carcinomatous meningitis
- Any prior systemic therapy for metastatic breast cancer
- Prior treatment with fulvestrant or any selective estrogen-receptor degrader, with the exception of patients that have received fulvestrant or any selective estrogen-receptor degrader as part of neoadjuvant therapy only and with treatment duration of no longer than 6 months
- Prior treatment with any PI3K, AKT, or mTOR inhibitor, or any agent whose mechanism of action is to inhibit the PI3K-AKT-mTOR pathway
- Appropriate for treatment with cytotoxic chemotherapy at time of entry into the study, as per national or local treatment guidelines (e.g., patients with visceral crisis)
- Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes
- Inability or unwillingness to swallow pills or receive IM injections
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:
  - Measurable disease outside the CNS
  - No ongoing requirement for corticosteroids as therapy for CNS metastases, with corticosteroids discontinued for $\geq$2 weeks prior to enrollment and no ongoing symptoms attributed to CNS metastases
  - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic assessments
  - Screening CNS radiographic assessments $\geq$4 weeks since completion of radiotherapy
  - No history of intracranial hemorrhage or spinal cord hemorrhage

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures biweekly or more frequently

  Indwelling pleural or abdominal catheters may be allowed, provided the patient has adequately recovered from the procedure, is hemodynamically stable and symptomatically improved.

- Serious infection requiring IV antibiotics within 7 days prior to Day 1 of Cycle 1
- Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
- Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye
- Requirement for daily supplemental oxygen
- Symptomatic active lung disease, including pneumonitis
- History of or active inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)

  Patients currently receiving immunosuppressants for inflammatory bowel disease (e.g., sulfasalazines) are considered to have active disease and are $thus$ ineligible.

- Any active bowel inflammation (including diverticulitis)
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

  Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.

- Clinically significant and active liver disease, including severe liver impairment (Child-Pugh Class B/C), viral or other hepatitis, current alcohol abuse, or cirrhosis
- Known HIV infection

  Sites should include an HIV test during screening, as allowed per local regulations.

- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, metabolic, or infectious disease) or any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or that renders the patient at high risk from treatment complications
- Chemotherapy, radiotherapy, or any other anti-cancer therapy within 2 weeks before randomization

- Investigational drug(s) within 4 weeks before randomization
- Prior radiotherapy to ≥25% of bone marrow, or hematopoietic stem cell or bone marrow transplantation
- Unresolved toxicity from prior therapy, except for hot flashes, alopecia, and Grade ≤2 peripheral neuropathy
- History of other malignancy within 5 years prior to screening, except for cancers with very low risk of recurrence including, but not limited to, appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer. The Medical Monitor is available for consultation.
- History of or active clinically significant cardiovascular dysfunction, including the following:
  - History of stroke or transient ischemic attack within 6 months prior to first dose of study treatment
  - History of myocardial infarction within 6 months prior to first dose of study treatment
  - New York Heart Association Class III or IV cardiac disease or congestive heart failure requiring medication
  - Uncontrolled arrhythmias, history of or active ventricular arrhythmia requiring medication
  - Coronary heart disease that is symptomatic or unstable angina
  - Congenital long QT syndrome or QT interval corrected through use of Fridericia's formula >470 ms demonstrated by at least two ECGs >30 minutes apart, or family history of sudden unexplained death or long QT syndrome
- Clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Chronic corticosteroid therapy of ≥10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Allergy or hypersensitivity to components of the inavolisib/placebo, palbociclib, or fulvestrant formulations
- Treatment with strong CYP3A4 inducers or strong CYP3A4 inhibitors within 1 week or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment (see Section 4.4.3 for examples)
- Pregnant, lactating, or breastfeeding, or intending to become pregnant during the study or within 60 days after the final dose of study treatment (based on local prescribing information for fulvestrant, patients may be advised to use an effective means of contraception for up to 2 years after the last dose of fulvestrant)

  Women of childbearing potential (including those who have had a tubal ligation) must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Major surgical procedure, or significant traumatic injury, within 28 days prior to Day 1 of Cycle 1 or anticipation of the need for major surgery during the course of study treatment
- Minor surgical procedures <7 days prior to first dose of study treatment

  Patients must have sufficiently recovered from surgery, including adequate wound healing.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind 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: inavolisib plus palbociclib and fulvestrant or placebo plus palbociclib and fulvestrant. Randomization will occur in a 1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm

Randomization will be stratified according to the following factors:

- Visceral disease (yes or no)
- Endocrine resistance (primary or secondary according to European Society for Medical Oncology Advanced Breast Cancer 4 (ESMO ABC4) guidelines [Cardoso et al. 2018])
- Geographic region (North America/Western Europe, Asia, other)

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

While inavolisib PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, inavolisib PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data since those patients are expected to receive placebo and not inavolisib. Laboratories responsible for performing study drug PK assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for inavolisib PK concentration except by request (e.g., to evaluate a possible error in dosing).

To optimize timelines for delivery of PK-related analyses, unblinded PK data may be released to selected clinical pharmacology personnel at the clinical cutoff date, prior to study unblinding.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are inavolisib or its placebo, palbociclib, and fulvestrant. *LHRH agonists, dexamethasone mouth rinse, and metformin are considered non-investigational medicinal products (NIMPs).*

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Inavolisib and Placebo

Inavolisib and its matched placebo will be supplied by the Sponsor as an immediate-release tablet formulation (3-mg and 9-mg). The 3-mg tablet is a greyish orange to brownish orange, round film-coated tablet and the 9-mg tablet is a greyish orange to brownish orange, oval film-coated tablet. The 3-mg and 9-mg tablets should be stored at or below 86°F (30°C) and protected from light. For information on the formulation and handling of inavolisib/placebo, see the pharmacy manual and/or the Inavolisib Investigator's Brochure.

4.3.1.2 Palbociclib

Palbociclib will be supplied by the Sponsor as hard gelatin capsules or immediate release, film-coated tablets containing 125 mg, 100 mg, and 75 mg palbociclib. For

additional information on the formulation, packaging, and handling of palbociclib, refer to the palbociclib package insert or SmPC.

4.3.1.3 Fulvestrant

Fulvestrant will be supplied by the Sponsor per country-specific requirements. For countries in which the Sponsor is supplying fulvestrant, it will be supplied in sterile, single-patient, prefilled syringes containing 50 mg/mL fulvestrant, as a 5-mL injection. For details regarding storage of fulvestrant, refer to the fulvestrant package insert or SmPC.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1 and illustrated in Figure 3.

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

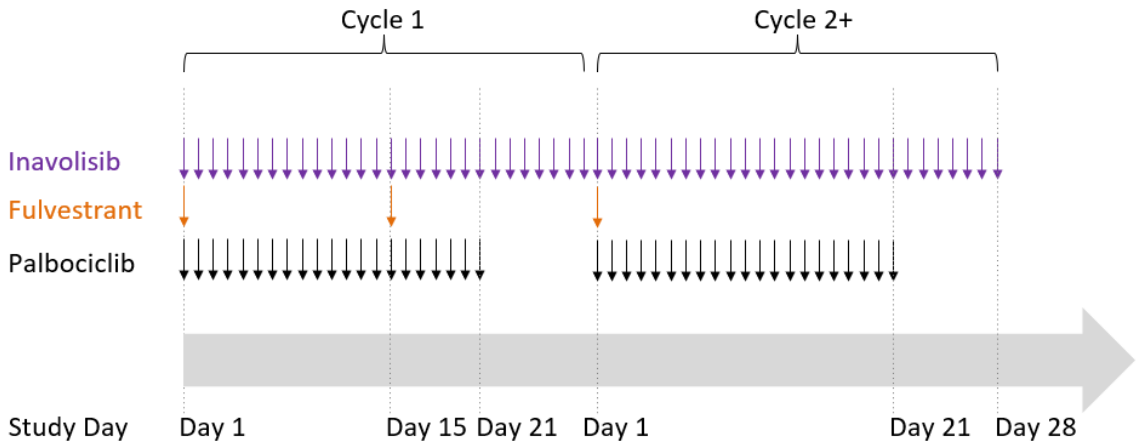
Mobile Nursing (MN) is only available at sites which have separately approved the use of the MN vendor; MN may not be conducted independently of the Sponsor-selected MN vendor. At applicable sites, study treatment may be administered by a trained mobile nurse at the patient's home, if the patient has provided written informed consent to participate in MN visits.

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

Guidelines for study treatment interruption, dosage modification, or discontinuation for patients who experience adverse events are provided in Sections 5.1–5.3.

It is recommended that patients keep a daily medication diary to assist them with compliance. Inavolisib/placebo tablets are to be taken daily; palbociclib capsules or tablets are taken 21 days on, 7 days off. Patients should return daily dosing diaries at each clinic visit as a conversation aid to inform site staff regarding dosing compliance. Note: dosing eCRFs should be completed using the prioritization of: i) site pharmacy drug accountability logs (IMP disbursed minus IMP returned), ii) clinic visit patient interview notes, and lastly iii) patient daily dosing diary.

Figure 3 Dosing Schedule for Inavolisib, Palbociclib, and Fulvestrant



4.3.2.1 Inavolisib and Placebo

Inavolisib/placebo will be administered orally QD on Days 1–28 of each 28-day cycle at a starting dose of 9 mg. Inavolisib/placebo will be administered in the clinic on Day 1 of Cycle 1, and on each subsequent cycle visit; it will be taken at home on all non-clinic visit days. Inavolisib/placebo should be taken at approximately the same time each day without regard to the timing of administration of food. If a dose is missed (not taken within 9 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up. For additional details, see Appendix 1.

4.3.2.2 Palbociclib

Palbociclib will be administered orally QD on Days 1–21 of each 28-day cycle (21 days on; 7 days off) at a starting dose of 125 mg. Palbociclib will be administered in the clinic on Day 1 of Cycle 1, and on each subsequent cycle visit; it will be taken at home on all non-clinic visit days. Palbociclib should be taken at approximately the same time each day, and should be taken with food to reduce the inter-patient variability of palbociclib exposure. If a dose is missed (not taken within 9 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up. Refer to the local prescribing information for more details (Ibrance® USPI and SmPC).

4.3.2.3 Fulvestrant

Fulvestrant 500 mg will be administered in the clinic as two IM injections of 250 mg each on Days 1 and 15 of Cycle 1. For subsequent cycles, patients will receive fulvestrant 500 mg (two IM injections of 250 mg each) in the clinic on Day 1 of each cycle, or approximately every 4 weeks. Refer to the local prescribing information for more details. It is recommended that fulvestrant be administered prior to the oral medications, inavolisib/placebo and palbociclib, during all clinic visits.

The fulvestrant dose level cannot be modified. In general, the investigator may consider continuing fulvestrant if the adverse event observed is thought to not be fulvestrant-related. See Sections 5.1.2.9 and 5.1.2.10 for guidelines for treatment interruption or discontinuation of fulvestrant.

4.3.2.4 Extended Cycle in the Event of a Palbociclib Hold due to an Adverse Event

In the event palbociclib administration is held due to an adverse event on Day 1 of a given cycle, the palbociclib dosing cycle should not begin until the patient is able to resume administration, which will correspond to a delayed Day 1 visit. All subsequent visits in that cycle will be based on the delayed Day 1 visit. As such, the cycle will be extended past 28 days. If appropriate, inavolisib/placebo administration may be continued daily, and fulvestrant administration may be continued approximately every 4 weeks, independently from the start of the palbociclib dosing cycle.

4.3.3 Non-Investigational Medicinal Products

4.3.3.1 LHRH Agonists

LHRH agonists are required beginning at least 2 weeks prior to initiation of study treatment for pre-/peri-menopausal women. For male patients, LHRH agonist therapy beginning at least 2 weeks prior to initiation of study is recommended. Acceptable agents include goserelin or leuprolide; triptorelin is also acceptable. Patients already on one of these three agents may remain on the same agent without switching. Every effort should be made to administer goserelin (given every 28 days) or alternative LHRH agonist as applicable on site at the time of fulvestrant administration in order to minimize the number of clinic visits. Where allowed per local standards, patients receiving LHRH agonists should be monitored (via follicle-stimulating hormone and/or estradiol level, as per local standards) approximately every 3 months for appropriate hormonal suppression; in cases of inadequate suppression, alternative hormonal suppression methods (e.g., ovarian ablation, as per local standards) must be considered.

4.3.3.2 Dexamethasone Mouth Rinse

If locally available, a compounded alcohol-free mouthwash of dexamethasone (0.5 mg in 5 mL) is recommended for prophylaxis or treatment of stomatitis/mucositis. As per the SWISH study (Rugo et al. 2017), patients may use 4 times daily for 8 weeks (10 mL swished for 2 minutes and spat) started concurrently with study treatment and/or used reactively with the first appearance of symptoms. No food or drink should be consumed for at least 1 hour after swishing and spitting the mouthwash. Additional mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal, and/or antibiotics) or topical corticosteroids (e.g., triamcinolone acetonide 0.05%–0.5%, fluocinolone acetonide 0.025%–0.05%, clobetasol propionate 0.025%) may be implemented. Diet should be modified (e.g., avoidance of spicy foods) and harsh mouthwashes (e.g., Listerine®) should be avoided.

4.3.3.3 Metformin

Patients experiencing hyperglycemia may require anti-hyperglycemic medication. The preferred first agent is metformin (see Section 5.1.2.2). At the investigator's discretion and where allowed by local regulations, prophylactic metformin may be initiated on Cycle 1, Day 1 for patients at high risk of hyperglycemia.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor where required by local regulations; local procurement of palbociclib and fulvestrant will be reimbursed in all other countries. 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.

Sponsor-supplied 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 Inventory Log; this includes all IMPs allocated to MN for delivery to and/or administration to enrolled patients utilizing home visits.

4.3.5 Continued Access to Inavolisib

The Sponsor will offer continued access to Roche IMP (inavolisib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (inavolisib) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP (inavolisib) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for HR+/HER2− breast cancer
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for HR/HER2– breast cancer
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

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

4.4.1 Permitted Therapy

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience toxicities should be treated symptomatically as clinically indicated.

Please also refer to the palbociclib local prescribing information regarding permitted therapies and recommended dose adjustments for concomitant medications.

Patients treated with anti-seizure medications or Vitamin K antagonist anticoagulation therapy (e.g., warfarin or similar agents) should have levels monitored regularly.

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

To reduce the risk of stomatitis, dexamethasone 0.5 mg/5mL alcohol-free mouthwash (10 mL swished for 2 minutes and spat, 4 times daily for 8 weeks), or alternative

mouthwash formulation (see Sections 5.1.1.2 and 5.1.2.3), may be started concurrently with study treatment. No food or drink should be consumed for at least 1 hour after swishing and spitting the mouthwash (Rugo et al. 2017).

Pain medications administered per standard clinical practice are acceptable while the patient is enrolled in the study and are to be recorded on the Analgesic Concomitant Medications eCRF.

Bisphosphonate or denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.

Multivitamins, calcium, and vitamins C, D, and E as supplements are allowed. However, due to the potential for drug-supplement interactions, and variability among suppliers and batches, the use of other dietary supplements is cautioned. The Sponsor's clinical pharmacology experts are available for advice on any specific supplements.

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

Co-administration of midazolam (sensitive CYP3A4 substrate) with multiple doses of palbociclib increased the midazolam plasma exposure by 61% in healthy subjects compared $with$ administration of midazolam alone. Therefore, the dose of a sensitive CYP3A4 substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) may need to be reduced, as palbociclib may increase its exposure (Ibrance USPI).

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

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

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is strongly discouraged because the pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited during the study and for at least 7 days prior to initiation of study treatment, unless otherwise specified 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 (including, but not limited to, chemotherapy, hormonal therapy, 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.
- Quinidine or other anti-arrhythmic agents
- 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 $\geq$3 months]), but who have developed brain metastases that are treatable with radiation, will be allowed to continue to receive therapy with inavolisib/placebo, palbociclib, and fulvestrant *in the* study until they either experience systemic progression of their disease and/or further progression in the brain (based on investigator assessments). Treatment with inavolisib and palbociclib should be held at least 24 hours in advance of palliative radiotherapy and until any effects or sequelae have resolved to Grade 1 or better. Patients should not miss more than one cycle of study treatment due to radiation treatment and must meet eligibility requirements to continue *in the* study treatment (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 patient 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 was included in the field of radiation, the lesion(s) will become unevaluable for tumor response.

  Further reasons for avoiding local radiotherapy include the difficulty in distinguishing new symptomatic pain or worsening of lytic bone lesions from disease progression. Time-to-Deterioration in Pain is a secondary endpoint of this study and Time-to-First-Skeletal-related-Event is an exploratory endpoint; palliative radiotherapy may alter these results. As such, palliative radiotherapy to bone in the absence of disease progression may be allowed after consultation with the Medical Monitor, however, such patients will be censored from the aforementioned

secondary and exploratory endpoints. Few clinical data are available about potential toxicities of radiation and treatment with inavolisib. Study treatment should be held ~24 hours prior to palliative radiotherapy and until any effects or sequelae have resolved to Grade ≤1. Patients should not miss more than one cycle of study treatment due to radiation treatment and must meet eligibility requirements to continue *in the* study treatment (Section 4.1.1). Previous clinical experience also suggests that new bone pain is frequently a symptom of disease progression. Bone pain secondary to fulvestrant treatment may be treated with pain medications, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids.

- Primary prophylactic use of hematopoietic growth factors (e.g., erythropoietins, granulocyte colony-stimulating factor [G-CSF], 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.
- Strong CYP3A4 inhibitors, including, but not limited to, the following: atazanavir, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, troleandomycin, itraconazole, ketoconazole, voriconazole, posaconazole, conivaptan, diltiazem, nefazodone, mibefradil, and grapefruit juice or grapefruit supplements. If co-administration of palbociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of palbociclib as per palbociclib local prescribing information.
- Strong CYP3A4 inducers, including, but not limited to, the following: rifampin, carbamazepine, phenytoin, oxcarbazepine, phenobarbital, nevirapine, hyperforin (St. John's Wort), and cyproterone

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

Drug Interactions Flockhart Table:

https://drug-interactions.medicine.iu.edu/MainTable.aspx

FDA Drug Interactions Table of Substrates, Inducers, and Inhibitors:

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

Enrolled patients who subsequently require the use of any prohibited therapies must be discontinued from study treatment and followed for safety outcomes for 30 days after

their last dose of study treatment, or until they receive another anti-cancer therapy, whichever occurs first.

4.4.4 Prohibited Food

Use of the following foods is prohibited as described below:

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

4.4.5 Additional Restrictions

No food or fluids other than water will be allowed from 8 hours prior to each study visit until after study laboratory samples are obtained. Once all scheduled study laboratory samples are collected, a snack or light meal is recommended as palbociclib capsules should be taken with food.

4.5 STUDY ASSESSMENTS

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

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity at each clinic visit and prior to each in-clinic dose of study treatment; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

At applicable sites, certain study activities/assessments may be performed by a mobile nurse at the patient's home in order to alleviate clinic site access restrictions during the COVID-19 pandemic, and to more generally improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services (MN vendor) for participating sites. Mobile Nursing is only available at sites which have separately approved the use of the MN vendor; MN may not be conducted independently of the Sponsor-selected MN vendor. The MN vendor is responsible for ensuring that all mobile nurses are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient provides signed informed consent to participate in MN visits, the MN network will initiate contact with the patient at the direction of the investigator's site. MN visits will be scheduled on specified visit days (Appendix 1), to allow relevant assessments to be performed by the mobile nurse. The schedule of activities (see Appendix 1) specifies the assessments that may be performed by a mobile nurse; assessments that have not been indicated for MN in Appendix 1 must not be performed by the mobile nurse.

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). Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of blood to assess biomarker eligibility by signing the prescreening consent form. The prescreening consent form also asks patients to submit available archival tumor tissue to enable diagnostic biomarker development. 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 and prescreening (if applicable) log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures; *staging data should be as per AJCC TNM version 8, found in* Appendix 12), reproductive status, and tobacco use 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 in accordance with the applicable laws (e.g., health authority requirements).

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

An assessment of the patient's ECOG Performance Status (see Appendix 9) will be completed at screening and as specified in the schedule of activities (see Appendix 1).

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Particular attention should be given to symptoms related to adverse events of special interest (see Section 5.2.3). Changes from baseline abnormalities should be recorded in patient notes. As part of tumor assessment,

physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Limited, symptom-directed physical examinations and ECOG Performance Status assessment may be performed by a mobile nurse according to the schedule of activities (Appendix 1).

4.5.4 Vital Signs

Vital signs will include measurements of height, weight, respiratory rate, pulse rate, blood oxygenation (pulse oximetry), 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.

Vital sign measurement may be performed by a mobile nurse according to the schedule of activities (Appendix 1).

4.5.5 Tumor and Response Evaluations

Response will be assessed by the investigator on the basis of physical examinations, CT scans, and other imaging modalities as clinically indicated, which may include brain imaging (CT or MRI), MRI scans, and/or bone scan, using RECIST v1.1 criteria (Appendix 11). 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 known sites of disease must be documented at screening (within 28 days prior to Cycle 1, Day 1) and re-assessed at each subsequent tumor evaluation.

At screening, diagnostic quality, contrast-enhanced CT scans of the chest, abdomen, and pelvis should be acquired. If IV contrast is contra-indicated, MRI scans of the abdomen and pelvis should be acquired along with a non-contrast CT scan of the chest. For metformin-treated patients undergoing CT scans with contrast, metformin should be held as per institutional standard-of-care. The same scan protocol should be followed at all subsequent tumor assessment timepoints, however, pelvic coverage may be considered optional if not clinically indicated and no pelvic disease is identified at baseline.

At screening, CT scans of the neck or extremities should be acquired if clinically indicated. At subsequent tumor assessment timepoints, scans should be acquired if disease was present at baseline or if clinically indicated.

At screening, bone scans or other institutional standard bone imaging should be acquired in all patients. Bone scan, positron emission tomography (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. The special considerations regarding the measurability of bone lesions are outlined in RECIST v1.1 (see Appendix 11). At subsequent tumor assessment timepoints, bone scans should be acquired if bone disease cannot be assessed by another modality, e.g., CT, if complete response is identified in target disease in patients with known bone disease, or if clinically indicated. If a bone scan cannot be performed during the course of the study due to, for example, a Technetium-99m shortage, alternative imaging options should be discussed with the Medical Monitor (e.g., sodium fluoride [NaF]).

At screening, a CT or MRI scan of the brain is required to confirm no progression in patients with previously treated brain lesions; the scan must be within the screening window and $\geq$ 4 weeks after the completion of radiotherapy. For all other patients, brain scans should be acquired if clinically indicated. At subsequent tumor assessment timepoints, brain scans should be acquired if disease was present at baseline or if clinically indicated.

A documented standard-of-care tumor assessment performed within 28 days prior to Cycle 1, Day 1 may be used for the screening assessment provided it meets the above requirements. Tumor assessments should be performed on schedule (approximately every 8 weeks [$\pm$7 days] for the first 2 years after randomization, and every 12 weeks [$\pm$7 days] thereafter) as described in Appendix 1, regardless of dose delay or early discontinuation, until disease progression. Patients who discontinue study treatment for any reason other than disease progression or death will continue to undergo tumor-response evaluations until progressive disease or the initiation of another anti-cancer therapy, whichever occurs first. At the investigator's discretion, scans may be repeated at any time if progressive disease is suspected.

Patients who have demonstrated control of their systemic disease (defined as having received clinical benefit [i.e., a PR, CR, or SD for $\geq$3 months]), but who have developed brain metastases that are treatable with radiation, will be allowed to continue to receive study treatment until they either experience systemic progression of their disease and/or further progression in the brain (based on investigator assessments).

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

- All lesions identified at baseline (target and non-target) are to be reassessed using the same method throughout the course of the study.

- All radiologic data (CT scans, MRI scans, bone scans, etc.) obtained for all patients enrolled at the center should be reviewed by the local radiologist who, together with the investigator, will determine the local assessment of response and progression.
- All radiologic data and photographs for skin lesions obtained at baseline, during the treatment period, and the follow-up period must be sent to a central imaging vendor contracted by the Sponsor within 2 weeks of imaging for BICR. Additional details regarding the BICR will be outlined in a separate charter.
- Tumor response and progression will be assessed and will be the basis for the efficacy analyses (along with survival information). The main analysis of the trial will be based on the local radiology review results. Objective responses will be confirmed by assessments performed $\geq$4 weeks after an initial documentation of response.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis. When noted, fasting samples should be collected after a minimum 8-hour fast.

- Hematology panel includes: RBC count, hemoglobin, hematocrit, reticulocyte count, platelet count, WBC count with differential count (neutrophils, bands [optional], eosinophils, basophils, monocytes, lymphocytes, other cells; i.e., must be sufficient for the determination of ANCs, lymphocytes). Reporting the differential as absolute counts is preferred, but percent is accepted.

  Fasting blood chemistry panel (serum or plasma) includes: sodium, potassium, chloride, bicarbonate # (or total carbon dioxide if considered standard-of-care for the region), BUN or urea, creatinine, glucose *, total protein, albumin, phosphate, calcium, magnesium, AST/SGOT, ALT/SGPT, total and direct bilirubin, and ALP. Laboratory samples should be drawn within 24 hours (all Cycle 1 and Cycle 2 visits) or within 48 hours prior to study drug administration at the clinic; glucose * is strongly preferred on the day of each clinic visit. Results for glucose, AST/SGOT, ALT/SGPT, bilirubin, and ALP should be reviewed prior to dosing.

  * Fasting glucose may also be obtained by glucometer (fingerstick); however, in the clinic these must also be confirmed with fasting blood glucose values.

  # For investigational sites in countries where bicarbonate (or carbon dioxide) is not collected as part of the standard blood chemistry panel, bicarbonate (or carbon dioxide) will not be measured.
- Fasting insulin
- Fasting lipid profile includes: total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides
- Amylase and lipase
- HbA1c
- Serum fibrinogen and coagulation (INR, aPTT, and PT)

Patients requiring Vitamin K antagonist anticoagulation therapy with warfarin or similar agents should have INR and aPTT monitored as clinically necessary to ensure appropriate anticoagulation.

- Urinalysis (dipstick allowed) panel includes: pH, specific gravity, glucose, protein, ketones, blood; and, if clinically indicated, microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Serum or 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 (see Appendix 1).

Samples for the following laboratory tests will be sent to a central laboratory or to the Sponsor for analysis:

- Plasma samples for PK analysis (see Section 6.6 and Appendix 2)

  Plasma samples collected during the study may be used for development of PK or biomarker assays, or endogenous substrate of drug metabolizing enzymes or drug transporters.
- Blood samples for biomarker NGS, except at sites in China
- Blood samples for whole genome sequencing (WGS) (unless prohibited by local regulatory authorities) (not applicable in China)

  Unless prohibited by the local regulatory authority, gene mutations will be assayed by WGS or other acceptable methodology such as multiplex PCR or allele-specific PCR. Results may be correlated to study treatment or other clinical measures to better understand the impact of genetic variants on drug metabolism, exposure, adverse events, and/or response.
- Biomarker assays in blood/plasma

  Blood samples will be collected from all patients at screening to determine *PIK3CA* mutation status using the F1LCDx assay (*see* Appendix 10) or the alternative, Sponsor-designated central laboratory for that region.

  Plasma samples will be collected at pre-defined timepoints during study treatment (see Appendix 1) and at the time of disease progression for exploratory biomarker research.
- Pre-treatment formalin-fixed paraffin embedded (FFPE) tumor tissue samples for central, retrospective *PIK3CA* mutation status determination as well as for other protocol-mandated exploratory biomarker assessments. Testing may be performed on tumor tissue from all screened patients (both enrolled patients and those who screen-fail based on the central test). Testing of patients' pre-treatment tumor tissue samples for *PIK3CA* mutation status may be used to establish performance characteristics of assays for diagnostic development. These additional data will have no impact *in the* study eligibility, and tumor tissue testing will be performed only after biomarker eligibility is established for each patient.

A representative FFPE block (preferred) or approximately 20 (25 preferred) slides containing unstained, freshly cut, serial tumor tissue sections will be required for enrollment eligibility purposes. If fewer than 20 slides are available, the patient may still be eligible for the study following consultation with the Sponsor.

Tumor tissue should be of good quality based on total and viable tumor content. The submitted specimen should preferably be from the same block used for any local *PIK3CA* mutation testing, if preexisting local test results will be reported to the Sponsor to determine eligible *PIK3CA* mutation status, and accompanied by the associated local pathology report. 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 types 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. A detailed description of tissue quality requirements and procedures for collection, handling, and shipping of the samples will be provided in a separate laboratory manual.

- Any patient, except those enrolled in China, may provide optional consent to submit tumor tissue collected during treatment and/or at the time of disease progression (see Appendix 1).

  Tissue submission guidelines for optional on-treatment and end-of-treatment biopsies should follow those for pre-treatment tumor biopsies, above. Please also refer to the laboratory manual.

  Note: It is preferred that a target lesion (TL) not be biopsied while *in the* study treatment; however, if there is no other viable lesion and a TL is biopsied, it must be treated in the same manner as a TL that has been included in a field of radiation (Section 4.4.3) and can no longer be eligible for tumor response. Such a TL must remain as a TL due to its inclusion at baseline and must subsequently be marked "Unable to Evaluate." As such, the Overall Assessments must also subsequently be "Unable to Evaluate" except in cases of PD or CR; PR and SD will no longer be possible for this patient.

Exploratory biomarker research may include, but will not be limited to, analysis of: gene and/or protein expression, soluble systemic chemokines and cytokines, the copy number and mutational landscape of cancer-related genes, gene expression signatures of mutations, etc. that are predictive of response to study treatment, are associated with disease progression, are associated with acquired resistance to study treatment, or that can increase the knowledge and understanding of breast disease biology and PI3K signaling. These studies may involve extraction of DNA, cell-free DNA (a.k.a. ctDNA), or RNA. Methodologies employed to complete these analyses may include, but will not be limited to, NGS, PCR, RNAseq, IHC, and proteomics-based approaches. NGS methods

may include WGS or whole exome sequencing (WES) of blood samples, but only at participating sites (see Section 4.5.10).

Next-generation sequencing may be performed by FMI or by the alternative, Sponsor-designated central laboratory in localities where FMI is not available. If performed by FMI, the investigator may obtain results through FMI's web portal. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The FMI NGS report is generated for research purposes only and is not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet criteria for testing or for samples that fail the testing process.

The investigator may obtain results through FMI's web portal for the following:

- FMI testing performed on the blood sample submitted in screening for biomarker eligibility or for central confirmation of a local blood test result
- FMI testing performed on tissue submitted from patients at the time of disease progression

For patients enrolling in localities without access to FMI, physicians may obtain a molecular testing result from the alternative, Sponsor-designated laboratory for the blood sample submitted in screening for biomarker eligibility or central confirmation.

FoundationOne Liquid CDx is a qualitative, NGS-based in vitro diagnostic test that uses high throughput hybridization-based capture technology for the detection of base substitutions, insertion and deletion alterations (indels), copy number alterations (CNAs), and select gene rearrangements in more than 300 cancer-related genes, as well as genomic signatures including tumor mutational burden (TMB) using ctDNA isolated from blood plasma. The assay has been launched in a CLIA- and CAP-accredited laboratory.

FoundationOne® CDx is a qualitative, NGS-based in vitro diagnostic test that uses high throughput hybridization-based capture technology for the detection of base substitutions, insertion and deletion alterations (indels), CNAs, and select gene rearrangements in more than 300 cancer-related genes, as well as genomic signatures including microsatellite instability and TMB using DNA isolated from FFPE tumor tissue specimens. The assay has been launched in a CLIA- and CAP-accredited laboratory.

Blood and urine sample collection may be performed by a mobile nurse in accordance with the schedule of activities (Appendix 1).

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

Unless the patient gives specific consent for 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 will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, and tissue samples collected for biomarker assessments and research will be destroyed no later than 15 years after the final Clinical Study Report has been completed. Samples collected for biomarker assessments in China will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled (e.g., screen failure), remaining archival tissue blocks will be returned to the site no later than 6–12 weeks after eligibility determination.

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

Data arising from sample analysis, including data on germline mutations, will be subject to the confidentiality standards described in Section 7.4.

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 FMI, in the specific cases outlined above. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy *in the* study data publication.

4.5.7 Ophthalmologic Examinations

Patients will undergo ophthalmic examinations at baseline during the screening period, at Cycle 6 (±2 weeks) during the study treatment period, at study treatment discontinuation, and based on any ocular disturbances. The ophthalmic examination should consist of a full ophthalmic exam with dilation and refraction with specific attention paid to lens examination and detailed documentation. In addition, patients will be asked if they have experienced any significant visual changes, pain, or sensitivity to light at each clinic visit. Any new eye-related symptoms including significant change in

vision, eye pain, or photophobia will be evaluated by an ophthalmologist. All clinically significant findings should be reported as Adverse Events.

4.5.8 Electrocardiograms

Triplicate 12-lead ECG recordings will be obtained at baseline to determine eligibility; otherwise, single 12-lead ECG recordings will be obtained at specified timepoints during study treatment, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as clinically indicated.

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

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. 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 QT interval corrected through use of Fridericia's formula based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

Clinically significant abnormalities observed during screening will be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities observed during the Study Treatment period will be recorded on the Adverse Event eCRF.

4.5.9 Clinical Outcome Assessments

Patient-reported outcome data will be collected to more fully characterize the clinical profile of inavolisib in combination with palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant in patients enrolled in the study. PRO data will be collected via electronic questionnaires at the clinic sites or patients' home using the following instruments: EORTC QLQ-C30, BR23, "worst pain" item from the BPI-SF, select items of the PRO-CTCAE, and the EQ-5D-5L. The questionnaires, translated into the local language as appropriate, will be distributed by the site staff or via secure web portal and completed in their entirety by the patient at baseline (Cycle 1, Day 1) and as noted in the schedule of activities (see Appendix 1).

In the event that after completion of the PROs at the start of a treatment cycle it is determined that the dose of palbociclib should be delayed, the Day 1 PROs will not be re-administered when the patient returns to the clinic following the delay. Additionally, the timing of subsequent PRO assessments (e.g., Day 15 during Cycles 2 and 3, and Day 1 of subsequent cycles after a delay) will be based on the actual Day 1 of the given cycle, when palbociclib was administered. For example, PROs will be completed at the *planned* Cycle 2, Day 1 visit prior to the actual office visit. In the event that the review of clinical laboratory results and adverse events (AEs) demonstrates that palbociclib should not be resumed at this visit (e.g., neutropenia), the actual Cycle 2, Day 1 visit will not occur until the patient is fit to resume palbociclib dosing. Frequently, this may require a 1-week delay. If appropriate, inavolisib and fulvestrant dosing may continue. PROs will not be repeated at the delayed Cycle 2, Day 1 visit when palbociclib dosing resumes. PROs will be administered at the new Cycle 2, Day 15, calculated from the resumption of palbociclib dosing.

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

Patient-reported outcome instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of study assessments, and prior to the administration of study treatment, unless otherwise specified. In cases where laboratory assessments (e.g., blood draws) are performed at a different location from the one providing treatment or where they are performed on a different day from study treatment administration, laboratory assessments can be completed before the completion of PROs as long as results have not been discussed with the patient.

Patient-reported outcome instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor or through a secured website. The device and the secured website will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device/secured website and instructions for completing the instruments electronically will be provided by the site staff. In cases where the electronic device cannot be used (e.g., patient is unable to visit the site in person or elects MN visit), the instruments can be administered through a secured website. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

During clinic visits and visits conducted by a mobile nurse (Appendix 1), 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 that is included on the electronic device, as provided by the Sponsor. Instruments must not be printed from the protocol and given to patients on paper.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 10–15 minutes at each visit specified in the schedule of activities (see Appendix 1).
- 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.

During the post-treatment follow-up period, patients may be contacted by site staff or a mobile nurse with a request to complete the PRO instruments at home through a website if they are not able to visit the site. Patients should be given the following instructions for completing PRO instruments at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.
- 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 EORTC QLQ-C30 (see Appendix 4) is a validated and reliable self-reported measure (Aaronson et al. 1993; Sprangers et al. 1996; Fitzsimmons et al. 1999). It consists of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), eight symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), financial difficulties, and GHS/HRQoL with a recall period of the previous week.

EORTC QLQ-BR23

The EORTC QLQ-BR23 breast cancer module 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.

BPI-SF "Worst Pain" Item

The BPI-SF is a widely used patient-reported outcome measure for assessing pain, and the "worst pain" item is frequently recommended for evaluating increases in the severity of pain (Cleeland 2009; Shi et al. 2009). The item asks patients to rate their pain at its worst in the last week on a scale from 0 to 10.

PRO-CTCAE

The PRO-CTCAE (see Appendix 7) is an item bank reflecting 78 symptomatic adverse events rated according to their severity, interference with daily function, frequency, and/or occurrence. The item bank was designed and validated as a repository of standalone items (Basch et al. 2014). PRO-CTCAE will be completed per the schedule of activities (see Appendix 1), if available in the patient's preferred language.

Only adverse events that are patient self-reportable (Basch et al. 2014) were selected for assessment in this study. Adverse events that rely on laboratory testing assessments (e.g., neutropenia, anemia) and that may frequently present as being primarily asymptomatic or with nonspecific signs and symptoms were disregarded. Adverse events that did not have an identifiable symptom equivalent in the PRO-CTCAE were also excluded. Based on the above criteria, 7 symptomatic adverse events that have been associated with inavolisib, palbociclib, or fulvestrant treatment were selected from the PRO-CTCAE item bank: diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash symptoms. An additional question providing an overall assessment of the burden of side effects will also be collected.

EQ-5D-5L

The EQ-5D-5L 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. 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. The EQ-5D-5L will be collected to inform pharmacoeconomic modeling and will be included only descriptively in the Clinical Study Report.

4.5.10 Blood Samples for Whole Genome Sequencing (Patients at Participating Sites)

At participating sites (where approved locally), blood samples will be collected for DNA extraction to enable WGS to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with acquired resistance to study treatment, 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 may aim to distinguish germline mutations from somatic mutations. The samples may be sent to one or more laboratories for analysis. WGS is not applicable in China.

Collection and submission of blood samples for WGS is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

Genomics are increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches, new methods for monitoring efficacy and safety, and/or new methods for 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 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).

See Section 4.5.6 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 Biopsies

Consenting patients will undergo optional tumor biopsies after treatment initiation between Days 15 and 22 (±1 day) of Cycle 1 and/or at disease progression and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Participation in "consent for optional biopsy collection" is not available in China. Samples collected via resection, core needle biopsy (three cores in the same block preferred), or excisional, incisional, punch, or forceps biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

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 4.5.6. See Section 4.5.6 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.12 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.

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

Sites in China are excluded from the “optional samples for research biosample repository” collection.

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 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 inavolisib, cancer, diseases, or drug safety:

- Leftover blood, serum, 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), including leftover blood and tumor tissue samples from medically indicated procedures performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. 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 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.

Research Biosample Repository 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

Research Biosample Repository 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 *in the* 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

Research Biosample Repository 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 she or he continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Intolerable toxicity related to study treatment determined by the investigator to be unacceptable given the potential for treatment benefit and the severity of the event
- Unequivocal disease progression per investigator assessment according to RECIST v1.1
- Symptomatic deterioration attributed to disease progression
- 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.

All patients will return to the clinic for a safety follow-up visit 30 (±7) days after the final dose of study treatment (see Appendix 1 for additional details).

Discontinuation from final study treatment is not discontinuation from the study. 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 3 months until death, unless the patient withdraws consent or the

Sponsor terminates the study. Patients that discontinue study treatment for reasons other than objective disease progression, withdrawal of consent, or death will continue to have tumor assessments performed every 8 weeks (±7 days) for the first 2 years after randomization and then every 12 weeks (±7 days) until documented disease progression or onset of new anti-cancer therapy, whichever occurs first.

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 withdrawal from the study may include, but are not limited to, the following:

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

Note that all patients are to be followed for survival following the discontinuation of study treatment, except in the cases noted above.

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. Patients will not be followed for any reason after consent has been withdrawn. 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, published obituaries, etc.), in accordance with local regulations, 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

Inavolisib is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on nonclinical and clinical experience with inavolisib in ongoing studies and clinical experience with other PI3K pathway inhibitors. The anticipated important safety risks for inavolisib are outlined below. Please refer to the Inavolisib Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients potentially at higher risk for toxicities due to one or more components of study treatment. 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. Safety assessments will include interval history since the previous assessment, physical examinations, and specific laboratory studies. All serious adverse events and adverse events of special interest (AESI) are to be reported in "real time" (within 24 hours of the event) via the electronic data capture (EDC) system. In addition, guidelines for managing adverse events, including criteria for treatment interruption, dosage modification, and/or treatment discontinuation, are provided below.

In addition to the Sponsor’s routine and real-time safety monitoring, an iDMC will be established that will operate according to a pre-specified iDMC charter (see Section 3.1.2). As an additional safety monitoring measure, an interim safety review will be performed after the enrollment of the first 25 patients and treatment for at least three cycles.

5.1.1 Identified and Potential Risks Associated with Inavolisib

On the basis of the established class effects of PI3K and mTOR inhibitors in patients with cancer, as well as nonclinical data and clinical experience from Study GO39374 with inavolisib, hyperglycemia, stomatitis/oral mucositis, rash, diarrhea/colitis, and pneumonitis are safety concerns for inavolisib. Given that these adverse events may require either dose interruptions and/or dose reductions or may have the potential to cause life-threatening conditions, close monitoring and a robust risk-mitigation strategy is warranted during the conduct of this Phase III study.

The combinations of inavolisib with palbociclib and letrozole and with palbociclib and fulvestrant are also being explored in Study GO39374. Results to date have shown good tolerability, with no additional safety signals beyond those associated with PI3K inhibitor class-effects and expected toxicities associated with each of the combination partners, palbociclib and letrozole or fulvestrant. Refer to the Inavolisib Investigator's Brochure for details.

5.1.1.1 Hyperglycemia

Effects on glucose and/or insulin metabolism are a known effect with PI3K inhibitors. Increased glucose was observed in rat and dog toxicology studies at all doses tested and appeared to be dose dependent. Hyperglycemia has been reported in patients receiving inavolisib and is an identified risk of inavolisib. Hence, diabetic patients and patients with elevated fasting glucose at baseline (fasting glucose ≥126 mg/dL [≥7.0 mmol/L] or HbA1c ≥6.0% [≥42 mmol/mol]) will be excluded from the study. Fasting glucose levels will be assessed at baseline, and fasting glucose levels will be monitored during the study, as outlined in Appendix 1. Patients should be advised to report symptoms associated with hyperglycemia such as polydipsia, polyuria, polyphagia, blurry vision, or symptoms associated with acidosis such as rapid or shallow breathing, confusion, fatigue, headache, or drowsiness.

The preferred first-line agent for the management of hyperglycemia is metformin; more detailed guidelines for study treatment dose modification, interruption or discontinuation (Table 1), and medical management for patients who experience hyperglycemia (Table 2) are provided in Section 5.1.2.2.

5.1.1.2 Stomatitis and Oral Mucositis

Treatment-related stomatitis/oral mucositis has been reported with the use of inavolisib. Stomatitis has also been reported in >10% of patients receiving palbociclib. Therefore, there is a concern for potential overlapping toxicity for the combination of inavolisib and palbociclib. Patients should be advised to report symptoms immediately. Intervention should begin at the earliest signs of oral mucosal inflammation. If locally available, a compounded alcohol-free mouthwash of dexamethasone (0.5 mg in 5 mL) is recommended for prophylaxis or treatment of stomatitis/mucositis. As per the SWISH study (Rugo et al. 2017), patients may use 4 times daily for 8 weeks (10 mL swished for 2 minutes and spat) started concurrently with study treatment, and/or used reactively with the first appearance of symptoms. Additional mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal, and/or antibiotics) or topical corticosteroids (e.g., triamcinolone acetonide 0.05%–0.5%, fluocinolone acetonide 0.025%–0.05%, clobetasol propionate 0.025%) may be implemented. Patients should avoid alcohol, hydrogen peroxide, iodine, or thyme-containing products, as they may exacerbate the condition. They should also avoid harsh mouthwashes (e.g., Listerine). Diet should be modified (e.g., avoidance of spicy foods). Guidelines for managing stomatitis and oral mucositis are provided in Table 4.

5.1.1.3 Potential Gastrointestinal Toxicities

In the 4-week toxicology study of inavolisib in dogs, gastrointestinal inflammation was observed. Thus, patients with inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, and active bowel inflammation (e.g., diverticulitis) will be excluded from this study. Diarrhea, nausea and vomiting have also been reported in $>10\%$ of patients receiving palbociclib. Therefore, there is a concern for potential overlapping toxicity for the combination of inavolisib and palbociclib. Gastrointestinal effects will be closely monitored by interval history and physical examination (see Appendix 1). Development of abdominal pain, nausea, vomiting, clinically significant changes in stool (e.g., diarrhea, bloody stools) may necessitate more frequent monitoring, and study drug may be held if symptoms are prohibitive for normal function. Clinical evaluation for infectious (e.g., *Clostridium difficile*, enteric bacteria, and cytomegalovirus) or inflammatory (e.g., inflammatory colitis) etiologies for diarrhea should be conducted. Guidelines for managing gastrointestinal toxicities *and inflammatory colitis* are provided in Table 6 *and Table 7, respectively*.

5.1.1.4 Potential Skin Disorders

Treatment-related rash has been reported for other PI3K inhibitors in clinical studies and is commonly manifested as a maculo-papular rash with or without pruritus. Rash has also been reported in $>10\%$ of patients receiving palbociclib. Therefore, there is a concern for potential overlapping toxicity for the combination of inavolisib and palbociclib. Rash and other dermatologic events should be closely monitored and managed per standard-of-care. Guidelines for management of rash, including dosage modification, are provided in Table 5.

When applicable, ad-hoc photographs of toxicities of the skin or the mucous membranes (i.e., rash or mucositis) may be taken and submitted to the Sponsor to allow further evaluation.

5.1.1.5 Potential Lung Inflammation/Pneumonitis

Lung inflammation was observed in the inavolisib 4-week dog study at the highest dose tested. This finding was observed only at a dose level considered not tolerable in this species. Interstitial lung inflammation/pneumonitis has been observed in clinical studies with other PI3K inhibitors. Rare but severe lung inflammation has been reported with CDK4/6 inhibitors, including palbociclib, when taken in combination with endocrine therapy. Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), any grade and Grade ≥ 3 events of interstitial lung disease (ILD)/pneumonitis were reported in 1.0% and 0.1% of patients treated with palbociclib, respectively. Although no fatal cases were reported from these studies, additional cases of ILD/pneumonitis with fatalities have been observed in the post-marketing setting. Therefore, there is a concern for potential overlapping toxicity for the combination of inavolisib and palbociclib. Specific management guidelines and guidance for holding or discontinuing therapy for symptomatic and asymptomatic pneumonitis based on the severity of pneumonitis are provided in Table 8.

5.1.1.6 Potential Immunosuppressant Effects

Immunosuppression and increased risk of infections are known to be associated with marketed PI3K-mTOR pathway inhibitors. Toxicology studies demonstrated decreases in reticulocytes, leukocytes, and absolute lymphocyte counts in animals treated with inavolisib. Thus, patients who are immunocompromised as the result of HIV or receiving immunosuppressive therapies will be excluded from this study. Patients will be monitored routinely for changes in circulating blood counts, including white cell differential, and should be monitored for fever and signs of infection.

5.1.1.7 Potential Reproductive Effects

Potential adverse effects on male reproductive function, including focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis, were observed in one or more dogs in the 4-week repeat-dose toxicity study. Focal inspissation of seminiferous tubule contents persisted in one animal at the end of the 4-week recovery period.

Patients should be notified of the possibility of reproductive sterility. In the event of patient concern and in accordance with local standards, Principal Investigators may opt to refer male patients for consultation with a local sperm preservation facility (i.e., sperm bank). Because of the unknown effects on human reproductive organs and gonadal cells, all male and female patients should use an effective means of contraception (e.g., abstinence, double-barrier method, surgical sterilization of partner) while taking inavolisib.

5.1.1.8 Potential Ocular Toxicities

In the 4-week toxicology study in rats, lens degeneration was observed in the highest inavolisib dose group (10 mg/kg; 4 of 30 rats). This finding was characterized by minimal-to-mild lens fiber swelling, separation of lens fibers and/or accumulation of subcapsular proteinaceous material. It is unclear whether the lens finding was a direct effect of inavolisib or an indirect effect secondary to marked hyperglycemia in this dose group. No inavolisib-related eye findings were observed in rats at lower doses. In dogs, ocular-related findings included inflammation and lens fiber swelling. In dogs administered 1.5/1.0 mg/kg inavolisib for 3 months, ocular inflammation was limited to focal, minimal neutrophilic infiltrates in the stroma of the corneal-limbal junction of the eye. In the 4-week study in dogs, neutrophilic infiltration in limbus and sclera, mild endophthalmitis, and low-grade uveitis were observed in the highest dose group (treated with 5 mg/kg and reduced to 3 mg/kg), a dose that was not considered tolerable. These findings were reversible and likely part of a systemic generalized inflammatory condition. In dogs administered $\geq$0.3 mg/kg inavolisib in the 3-month toxicity study, bilateral, reversible, very slight swelling of the fibers at the equatorial region of the lens was observed in one male and one female at 0.3 mg/kg, and one male and one female at 1.5/1.0 mg/kg. Although lens fiber swelling may be a result of changes in lens osmotic pressure associated with hyperglycemia present at 1.5/1.0 mg/kg in this study, since hyperglycemia was not observed in animals at 0.3 mg/kg, a direct inavolisib effect

cannot be ruled out. The clinical relevance of these ocular findings to humans is unknown.

Patients with any concurrent ocular or intraocular condition, such as cataract or diabetic retinopathy, that would require medical or surgical intervention during the study period to prevent or treat vision loss, will be excluded from the study. In addition, patients with active uveitis or vitritis, history of uveitis, or active infectious process in the eye will also be excluded from the study. Patients will undergo ophthalmic examinations at baseline during the screening period, at Cycle 6 during the study treatment period, at study treatment discontinuation, and based on any ocular disturbances. The ophthalmic examination should consist of a full ophthalmic exam with dilation and refraction with specific attention paid to lens examination and detailed documentation. During study treatment, hyperglycemia will be managed according to the guidelines in Table 2. In addition, patients will be asked if they have experienced any significant visual changes, pain, or sensitivity to light at each clinic visit. Any new eye-related symptoms including significant change in vision, eye pain, or photophobia will be evaluated by an ophthalmologist.

5.1.1.9 Drug–Drug Interactions

In vitro data suggest that inavolisib is metabolized by CYP3A4 and that there is a low-to-moderate potential for DDI with any medication that strongly inhibits or induces this enzyme. In addition, in vitro data suggest that inavolisib is a substrate of the efflux transporter P-glycoprotein. Palbociclib is extensively metabolized by CYP3A4. Co-administration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%, and co-administration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85%. Therefore, strong CYP3A4 inhibitors and inducers are prohibited in this study (see Section 4.4.3).

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications of Inavolisib/Placebo

The inavolisib/placebo dose reduction instructions provided in Table 1 are intended to serve as recommended guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while monitoring patient safety. These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases. In addition to these guidelines, more conservative drug interruptions or dose reductions for the management of adverse events are permitted at the discretion of the investigator when deemed to be in the best interest of the patient. In general, decisions on interruption of any of the study treatment components (inavolisib/placebo, palbociclib, fulvestrant) should be made independently of the others; that is, one study treatment component alone may be interrupted for adverse events associated with that medication without mandatory interruptions of the other study treatment components.

Dose modification for adverse events should be taken first with inavolisib rather than palbociclib unless clearly attributable to palbociclib alone based on known toxicity profile and the investigator's assessment. When an adverse event is clearly attributed to palbociclib, dose modification of palbociclib alone based on its known toxicity profile and the investigator's assessment is allowed. For toxicities attributed to the combination of inavolisib, palbociclib and fulvestrant, it is preferred to initially modify the dosage of one drug (i.e., inavolisib or palbociclib), then modifying the other drug (e.g., if inavolisib dose was reduced but toxicity persisted or recurred, then reduce the dose of palbociclib), depending upon the nature and severity of the toxicity. Further dose de-escalation may be considered if the same toxicity arises.

Table 1 Overall Dose Modification Guidelines for Inavolisib-Related Adverse Events

	Inavolisib/placebo
Starting dose	9 mg QD
First reduction	6 mg QD
Second reduction	3 mg QD [a]

QD = once daily.

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

The investigator may temporarily suspend inavolisib/placebo dosing due to an inavolisib-related toxicity or an unanticipated medical event not associated with study treatment toxicity or with disease progression. Dose interruptions for any component of study treatment should not exceed one cycle (i.e., approximately 28 days); patients withheld from treatment beyond 28 continuous days are expected to be withdrawn from study treatment. However, the Medical Monitor is available to advise extension for extenuating circumstances. Depending on the nature and the severity of the inavolisib-related toxicity, the investigator may resume inavolisib/placebo dosing in the patient at the same dose or at one dose level lower (as detailed in Table 9). Dose re-escalation of inavolisib/placebo is permitted only after a thorough benefit-risk evaluation by the investigator; the Medical Monitor is available for consultation as needed.

5.1.2.2 Management of Hyperglycemia

The anti-hyperglycemic agent metformin should be used first-line for the management of sustained fasting glucose > 160 mg/dL or > 8.9 mmol/L or anytime fasting glucose is > 250 mg/dL or > 13.9 mmol/L. Investigators should exercise caution in the dosing and management of patients receiving metformin in combination with inavolisib and must be vigilant for signs of renal impairment and metformin toxicity (see also Section 5.1.1.2). Patients administered metformin should be cautioned and monitored for signs of intolerance or toxicity, including lactic acidosis, which may occur in the setting of acute

worsening of renal function or cardiorespiratory illness or sepsis and can be life-threatening. The most frequently reported adverse events with metformin are nausea, vomiting, diarrhea, abdominal pain, and loss of appetite. Metformin does not produce hypoglycemia, but it may occur with a missed meal, alcohol consumption, heavy exercise, or when it is taken with another type of diabetes medicine.

In the event metformin is not tolerated or not sufficient, another anti-hyperglycemic medication(s) may be added to or used in place of metformin. Preferred agents include sodium glucose co-transporter 2 (SGLT2) inhibitors, pioglitazone, and dipeptidyl peptidase-4 inhibitors, where available and considered appropriate by investigators. If SGLT2 inhibitors are prescribed, ensure adequate hydration and monitor for vaginal yeast infections. Patients administered pioglitazone should be monitored closely for signs of heart failure including fluid retention or edema. Patients administered insulin or sulfonylureas should be treated with caution when these agents are used to manage hyperglycemia and inavolisib is subsequently interrupted or discontinued: this can lead to rapid escalation of insulin levels and risk of hypoglycemia. For each of these agents, refer to the local prescribing information for additional information.

Patients at risk for developing hyperglycemia (e.g., pre-diabetes, body mass index greater than or equal to 30 kg/m^2, hemoglobin A_{1c} greater or equal to 5.7%, over 45 years of age, family history of diabetes, history of gestational diabetes, and any other factor that may lead to increased risk of developing hyperglycemia, including certain ethnicities, inactive lifestyle, may initiate treatment with metformin on Day 1 of the study, where allowed by local regulations. Table 2 describes management guidelines of hyperglycemia and Table 3 presents proactive mitigation recommendations for patients with risk factors for hyperglycemia. In addition, any patient may be instructed to utilize a glucometer to monitor fasting glucose at home on a daily basis at the treating investigator's discretion.

Table 2 Management of Hyperglycemia

Fasting Glucose Values	Action to be Taken
> ULN to 160 mg/dL (8.9 mmol/L)	• Encourage patients to adopt a diabetic diet. • Consider consultation with endocrinologist or diabetologist. • Provide home glucose monitoring to high risk patients and educate to check fasting glucose at home. [a] • Consider oral anti-diabetic medications (e.g., metformin) for high risk patients. [a] • Recheck in 3 days and adjust medications as needed. [b] • Continue current dose level of inavolisib/placebo.
> 160 to 250 mg/dL (> 8.9–13.9 mmol/L)	• Interrupt inavolisib/placebo dose until hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L. [f] • Start or increase dose for an oral anti-diabetic medication (e.g., metformin, SGLT2 inhibitor). [c] • Recheck in 3 days and adjust or add anti-diabetic medications as needed. [b] • Encourage patients to adopt a diabetic diet. • Consider consultation with endocrinologist or diabetologist. • Initiate fasting home glucose monitoring. • Resume current dose level of inavolisib/placebo when hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L. • If fasting blood glucose persists > 200–250 mg/dL or > 13.9–27.8 mmol/L for 7 days despite above interventions, discuss with the Medical Monitor. [f]

Table 2 Management of Hyperglycemia (cont.)

Fasting Glucose Values	Action to be Taken
> 250 to 500 mg/dL (> 13.9–27.8 mmol/L)	• Interrupt inavolisib/placebo. • Manage hyperglycemia as per standard-of-care. [c, d] • Start or increase dose for an oral anti-diabetic medication (e.g., metformin, SGLT2 inhibitor). [c] • Recheck in 3 days and adjust or add anti-diabetic medications as needed. [b] • Encourage patients to adopt a diabetic diet. • Consider consultation with endocrinologist or diabetologist. • Initiate fasting home glucose monitoring. • If hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L within 7 days, may resume at current dose level of inavolisib/placebo. • If hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L in ≥ 8 days, reduce inavolisib/placebo dose by one dose level when treatment resumes. [e] • If hyperglycemia > 250–500 mg/dL or > 13.9–27.8 mmol/L recurs within 30 days, reduce inavolisib/placebo dose by one dose level. [e]
> 500 mg/dL (> 27.8 mmol/L)	• Interrupt inavolisib/placebo. • Manage hyperglycemia as per standard-of-care. [c, d] • Assess for volume depletion and ketosis and administer appropriate intravenous or oral hydration. • Start or increase the dose for an oral anti-diabetic medication (e.g., metformin, SGLT2 inhibitor). [c] • Recheck in 3 days and adjust or add anti-diabetic medications as needed. [b] • Encourage patients to adopt a diabetic diet. • Consider consultation with endocrinologist or diabetologist. • Initiate fasting home glucose monitoring. • When hyperglycemia resolves to ≤ 160 mg/dL or 8.9 mmol/L, reduce inavolisib/placebo dose by one dose level when treatment resumes. [e] • If hyperglycemia > 500 mg/dL or > 27.8 mmol/L recurs within 30 days, permanently discontinue inavolisib/placebo.

Table 2 Management of Hyperglycemia (cont.)

SGLT2 = sodium glucose co-transporter 2; = ULN upper limit of normal.

[a] High-risk factors for diabetes include pre-diabetes, overweight, obese, body mass index greater or equal to 30 kg/m^2, hemoglobin A_{1c} greater or equal to 5.7%, over 45 years of age, family history of diabetes, certain ethnicities, inactive lifestyle, and history of gestational diabetes.

[b] Fasting glucose should be checked by finger stick or lab value (if patient has scheduled appointment) **PRIOR** to dosing. Oral anti-diabetic medications should be titrated to the maximum allowed dosages to achieve control of blood glucose to $\leq$160 mg/dL or 8.9 mmol/L. For example, metformin may be administered to a maximum dose allowed as per local prescribing information, given in divided doses, as tolerated. Please see local prescribing information of individual oral anti-diabetic agent for dosing guidelines.

[c] There is a risk of hypoglycemia if insulin or sulfonylureas are used, particularly if these agents are started during periods of inavolisib exposure and doses are not adjusted appropriately during periods of treatment interruption, during which patients' insulin sensitivity may increase rapidly. Short-term insulin is allowed to control blood glucose levels, but goal should be to maintain on oral agents once acute episode resolves.

[d] It is recommended that the patient is reassessed within 24 hours and preferably the same day for assessments of hydration status and renal function.

[e] A maximum of two dose reductions will be allowed.

[f] If, in the investigator's opinion, the benefit-risk assessment favors continued inavolisib dosing without interruption, inavolisib may be continued without interruption upon discussion with Medical Monitor once patients are managed on anti-diabetic agent(s) and fasting glucose $\leq$200 mg/dL [$\leq$11.1 mmol/L]. It is recommended that patients be instructed to utilize a glucometer to monitor fasting glucose and to call the clinic if fasting glucose $>$200 mg/dL [$>$11.1 mmol/L] prior to inavolisib dosing at home.

Table 3 Additional Management Guidelines for Patients at High Risk of Hyperglycemia

Patient Characteristics	Guidelines
• Hemoglobin A1c ≥ 5.7% to < 6.4% • Pre-diabetes • Body mass index ≥ 30 kg/m^2 • ≥ 45 years of age • Family history of diabetes • History of gestational diabetes • Any other factor that increases the risk of hyperglycemia (e.g., certain ethnicities such as African American, South Asian; sedentary lifestyle)	• Patient may be instructed to utilize a glucometer to monitor fasting glucose at home on a daily basis at the treating investigator's discretion. • Recommend moderate lifestyle changes such as: Dietary advice (e.g., small frequent meals, low carbohydrate content, high fiber, balanced carbohydrate intake over the course of the day, three small meals and two small snacks rather than one large meal, avoiding drinking sugar-sweetened beverages and switch to water whenever possible) Increase daily physical activity and exercise • Consultation with an endocrinologist or diabetologist is highly recommended. • Consider initiating prophylactic treatment with metformin (on Cycle 1 Day 1) in patients with more than one risk factor, where allowed by local regulations and at the investigator's discretion.

5.1.2.3 Management of Stomatitis/Oral Mucositis

For any grade stomatitis/mucosal inflammation, aggressive mouth care should be implemented early to help manage or prevent symptoms. If locally available, a compounded alcohol-free mouthwash of dexamethasone (0.5 mg in 5 mL) is recommended for prophylaxis or treatment of stomatitis/mucositis. As per the SWISH study (Rugo et al. 2017), patients may use 4 times daily for 8 weeks (10 mL swished for 2 minutes and spat) started concurrently with study treatment, and/or used reactively with the first appearance of symptoms. No food or drink should be consumed for at least 1 hour after swishing and spitting the mouthwash. Additional mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal, and/or antibiotics) or topical corticosteroids (e.g., triamcinolone acetonide 0.05%–0.5%, fluocinolone acetonide 0.025%–0.05%, clobetasol propionate 0.025%) may be implemented. Patients should avoid alcohol, hydrogen peroxide, iodine, or thyme-containing products, as they may exacerbate the condition. Diet should be modified (e.g., avoidance of spicy foods) and harsh mouthwashes (e.g., Listerine) should be avoided. Table 4 describes management of stomatitis/oral mucositis.

Table 4 Management of Stomatitis/Oral Mucositis

Grade of stomatitis/oral mucositis	Action to Be Taken
Any Grade	• Intervene early. • Initiate aggressive mouth care that includes dexamethasone (0.1 mg per mL) alcohol-free mouthwash. If that is not available, consider other mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics). • Avoid alcohol-, hydrogen peroxide-, iodine-, or thyme-containing products, as they may exacerbate the condition. Avoid harsh mouthwashes (e.g., Listerine®). • Diet should be modified (e.g., avoidance of spicy foods).
Grade 1: Asymptomatic or mild symptoms; intervention not indicated	• Initiate management as above. • Monitor symptoms and compliance with oral regimen. • Re-evaluate within 48–72 hours.
Grade 2: Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	• Interrupt inavolisib/placebo and manage as above until Grade ≤ 1. • When stomatitis/oral mucositis improves to Grade ≤ 1, resume dosing at the same dose. • For recurrent Grade 2 stomatitis or oral mucositis within 30 days, reduce inavolisib/placebo dose by one dose level.
Grade 3: Severe pain; interfering with oral intake	• Interrupt inavolisib/placebo until Grade ≤ 1 and reduce inavolisib/placebo dose by one dose level when dosing is resumed. • Interrupt palbociclib until recovery to Grade ≤ 2; then may resume palbociclib as per local prescribing information [a] (see Table 11 below).
Grade 4: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue inavolisib/placebo. • Manage palbociclib as per local prescribing information (see Table 11 below).

[a] Consider whether event is due to inavolisib, palbociclib, or both. Initial dose modification(s) should be made to the agent(s) contributing to event and if unknown, consider adjusting both.

5.1.2.4 Management of Rash

Patients with severe rash should also be monitored for associated signs and symptoms, such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. Permanently discontinue treatment for any rash with concurrent signs/symptoms strongly suggestive of a severe Type I hypersensitivity or anaphylactic/anaphylactoid reaction or with painful desquamation or mucosal involvement suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis or with other life-threatening complications. Dermatological consultation is recommended. Guidelines for management of rash are provided in Table 5.

Table 5 Management of Rash

Grade	Action to Be Taken
Grade 1	• Continue inavolisib/placebo dosing and monitor for changes in severity. • Consider prescribing topical corticosteroids [a] and/or antihistamines.
Grade 2	• Interrupt inavolisib/placebo treatment. • Treat rash per standard-of-care, including topical and/or oral corticosteroids [b] and/or antihistamines. • When rash resolves to Grade ≤1, resume inavolisib/placebo at the same dose or one dose level lower per investigator evaluation. • If Grade 2 rash recurs within 30 days, reduce inavolisib/placebo by one dose level when treatment resumes.
Grade 3	• Interrupt inavolisib/placebo treatment. • Interrupt palbociclib treatment until recovery to Grade ≤2 and manage as per local prescribing information (see Table 11 below).[c] • Treat rash with topical and/or systemic corticosteroids (oral or IV) and antihistamines. • If rash resolves to Grade ≤1 within 30 days, reduce inavolisib/placebo by one dose level when treatment resumes. • If rash does not resolve to Grade ≤1 within 30 days, discontinue inavolisib/placebo. • Refer to dermatologist for consultation and skin biopsy.

IV = intravenous.

[a] Suggested topical steroids include hydrocortisone 2.5% to face 2×daily, triamcinolone 0.1% or fluocinonide 0.1% cream to body 2×daily.

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

[c] Consider whether event is due to inavolisib, palbociclib, or both. Initial dose modification(s) should be made to the agent(s) contributing to event and if unknown, consider adjusting both.

5.1.2.5 Management of Diarrhea

Table 6 Management of Diarrhea

Grade	Action to Be Taken
Grade 1	• Adequate treatment with anti-diarrheals [a] and maximum supportive care. [b]
Grade 2	• Adequate treatment with anti-diarrheals [a] and maximum supportive care. [b] • Close monitoring. • Interrupt inavolisib/placebo until recovery to Grade ≤1, then may resume at the same dose. • If recurs within 30 days, reduce inavolisib/placebo by one dose level.
Grade 3	• Interrupt inavolisib/placebo until recovery to Grade ≤1, then reduce by one dose level. • Interrupt palbociclib treatment until Grade ≤2 and manage as per local prescribing information (see Table 11 below). [c] • Manage as per Grade 2 diarrhea guidelines. • If recurs within 30 days after initiation of the first dose reduction, reduce inavolisib/placebo by one dose level. If recurs within 30 days from the second dose reduction, permanently discontinue inavolisib/placebo.
Grade 4	• Permanently discontinue inavolisib/placebo • Manage palbociclib as per local prescribing information (see Table 11 below)

[a] Initiate loperamide (Imodium®) dose with 4 mg, then 2 mg every loose stool up to 16 mg/day. May consider using combination of loperamide and Lomotil® (diphenoxylate and atropine) or codeine phosphate. Monitor closely for dehydration or constipation. May initiate second-line therapy (e.g., octreotide) if Grade ≥2 diarrhea persists after 48 hours of treatment with loperamide and/or Lomotil.

[b] Supportive care: initiate appropriate dietary modification, hydration therapy, and electrolyte supplements when clinically indicated. Dietary modification includes: stop all lactose-containing products and eat small meals; encourage adequate hydration with salt-containing liquids such as broth or Gatorade®.

[c] Consider whether event is due to inavolisib, palbociclib or both. Initial dose modification(s) should be made to the agent(s) contributing to event and if unknown, consider adjusting both.

5.1.2.6 Management of Inflammatory Colitis

Table 7 Management of Inflammatory Colitis

Grade	Action to Be Taken
Grade 1	• Close monitoring and treat as appropriate.
Grade 2	• If colitis-related symptoms do not improve to Grade ≤1 after 48 hours of anti-diarrheals, start treatment with oral corticosteroid. [a] • Interrupt inavolisib/placebo until recovery to Grade ≤1, then may resume at the same dose or one dose level lower per investigator evaluation. • If recurs within 30 days, reduce inavolisib/placebo by one dose level.
Grade 3	• Treat with high dose corticosteroids (IV solumedrol or PO prednisone). [b] • Interrupt inavolisib/placebo until recovery to Grade ≤1, then reduce by one dose level. • Hold palbociclib until recovery to Grade ≤1 and manage as per local prescribing information (see Table 11 below). • Consider colonoscopy. • If Grade 3 recurs, permanently discontinue inavolisib/placebo.
Grade 4	• Permanently discontinue inavolisib/placebo. • Manage palbociclib as per local prescribing information (see Table 11 below).

IV = intravenous; PO = by mouth; QD = once daily.

[a] 20–40 mg prednisone PO QD (starting dose).

[b] For severe grades, may also consider IV solumedrol 16–20 mg every 8 hours, or prednisone 60–80 mg PO QD equivalent to start.

5.1.2.7 Management of Pneumonitis

Table 8 Management of Pneumonitis

Grade	Intervention	Investigation	Inavolisib and Palbociclib Dose Modification and Management
Grade 1	• No specific therapy required	• Chest CT scan. • Repeat CT at least every 8 weeks until return to baseline. • Consider pulmonologist/ respirologist consult. • Advise patient to promptly report new or worsening respiratory symptoms.	• No action.
Grade 2	• Prescribe corticosteroids if infectious etiology is ruled out. • Taper as clinically indicated.	• Chest CT scan. • Repeat CT at least every 8 weeks until return to baseline. • Consider PFTs. • Obtain pulmonologist/respirologist consult.	• Hold inavolisib/placebo and palbociclib as long as corticosteroids are being given. When pneumonitis improves to Grade $\leq$ 1 and upon completion of any corticosteroid treatment, resume inavolisib/placebo and palbociclib dosing at the same dose or one dose level lower per investigator evaluation. For recurrent Grade 2 event, resume inavolisib/placebo and palbociclib dosing at one dose level lower.
Grade 3	• Prescribe corticosteroids if infectious etiology is ruled out. • Taper as clinically indicated.	• Chest CT scan. • Repeat CT at least every 8 weeks until return to baseline. • Consider PFTs and bronchoscopy. • Obtain pulmonologist/ respirologist consult.	• Hold inavolisib/placebo as long as corticosteroids are being given. When pneumonitis improves to Grade $\leq$ 1 and upon completion of any corticosteroid treatment, resume inavolisib/placebo dosing at one dose level lower. • Permanently discontinue palbociclib.

Table 8 Management of Pneumonitis (cont.)

Grade 4	• Prescribe corticosteroids if infectious etiology is ruled out. • Taper as clinically indicated.	• Chest CT scan. • Repeat CT at least every 8 weeks until return to baseline. • Consider PFTs. • Obtain pulmonologist/ respirologist consult • Bronchoscopy is recommended.	• Permanently discontinue inavolisib/placebo. • Permanently discontinue palbociclib.

CT = computed tomography (scan); PFTs = pulmonary function tests

5.1.2.8 Management of Other Clinically Significant Adverse Events

Inavolisib may be continued without interruption for uncomplicated Grade 3 hematologic toxicities with the exception of neutropenic fever where inavolisib should be interrupted until neutrophil count recovers to Grade ≤ 2. Inavolisib then may resume at same dose.

For uncomplicated Grade 4 neutropenia, inavolisib may be continued without interruption. Interrupt inavolisib for Grade 4 thrombocytopenia until recovery to Grade ≤ 2, and then resume inavolisib at same dose.

See Table 9 for inavolisib/placebo dose modifications for other clinically significant adverse events attributed to inavolisib.

Table 9 Inavolisib/Placebo Dose Delay and Modification Guidelines for Other Clinically Significant Adverse Events Attributed to Inavolisib

Grade	Inavolisib/Placebo
Grade 3, first event	• Hold inavolisib/placebo until Grade ≤ 1. • Resume inavolisib/placebo at the same dose or one dose level lower per investigator evaluation.
Grade 3, recurrent or Grade 4, non–life-threatening	• Hold inavolisib/placebo until Grade ≤ 1. Resume inavolisib/placebo dosing at one dose level lower.
Grade 4, life-threatening	• Permanently discontinue inavolisib/placebo. • Single-agent fulvestrant may be continued per investigator evaluation.

5.1.2.9 Safety Monitoring for Fulvestrant

Fulvestrant is an ER antagonist indicated for the treatment of HR-positive metastatic breast cancer in postmenopausal women and for the treatment of HR-positive, HER2-negative metastatic breast cancer in combination with palbociclib in patients with

disease progression after endocrine therapy. There are no expected significant overlapping toxicities between inavolisib and fulvestrant.

The common adverse events associated with the use of fulvestrant include hypersensitivity reactions, hot flushes, nausea, elevated hepatic enzymes (ALT, AST, ALP), rash, joint and musculoskeletal pain, asthenia, injection site reactions, urinary tract infections, reduced platelet count, anorexia, headache, venous thromboembolism, vomiting, diarrhea, elevated bilirubin, back pain, vaginal hemorrhage, peripheral neuropathy, and sciatica. In randomized studies with fulvestrant, injection site pain was commonly reported. Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

Fulvestrant should be used with caution in patients with mild to moderate hepatic impairment. Fulvestrant should be used with caution in patients with severe renal impairment (creatinine clearance <30 mL/min).

Refer to the fulvestrant local prescribing information for additional information.

5.1.2.10 General Guidance of Dose Modifications or Delays for Fulvestrant

The fulvestrant dose level cannot be modified. In general, the investigator may consider continuing fulvestrant if the observed adverse event is not thought to be fulvestrant-related. Decisions on interruption of any of the study treatment components (inavolisib/placebo, palbociclib, fulvestrant) should be made independently of the other study treatment components (i.e., one study treatment component alone may be interrupted for adverse events associated with that medication without mandatory interruptions of the other study treatment components).

If a scheduled dose coincides with a holiday or inclement weather or other conditions that preclude dosing, dosing should commence on the nearest following date, and subsequent dosing can continue on a new 28-day schedule on the basis of the new IM injection date.

5.1.2.11 Safety Monitoring for Palbociclib

In the Phase III PALOMA-3 study of palbociclib plus fulvestrant compared with fulvestrant, hematological Grade ≥ 3 adverse events observed in patients who received palbociclib plus fulvestrant were neutropenia (65%), leukopenia (28%), anemia (3%), and thrombocytopenia (3%). Febrile neutropenia was reported in 1% of patients. Granulocyte-CSF support was reported in 12% of patients treated with palbociclib plus fulvestrant compared with 1% of patients who received placebo plus fulvestrant. Non-hematological Grade ≥ 3 adverse events were observed in 2% or less of patients. In the palbociclib plus fulvestrant arm, dose interruptions and cycle delays occurred in 54% and 36% of patients, respectively. At least one dose reduction of palbociclib due to

an adverse event was observed in 34% of patients. Permanent discontinuation due to adverse events was 4% in the palbociclib plus fulvestrant arm (Verma et al. 2015; Cristofanilli et al. 2016).

In addition, an increase in the rate of infections and events of pulmonary embolism have been reported with palbociclib combination therapies.

Patients will have complete blood counts assessed prior to the start of palbociclib and will be monitored frequently throughout the study and as clinically indicated.

For hematologic toxicities assessed by the investigator as related to palbociclib, suggested guidelines for palbociclib dose modification are shown in Table 10. Refer to the palbociclib local prescribing information for additional information. See Section 5.1.2.8 for inavolisib management guidelines.

Table 10 Palbociclib Dose Modification and Management: Hematologic Toxicities

CTCAE Grade	Dose Modification
Grade 1 or 2	• No dose adjustment is required.
Grade 3	• Day 1 of any cycle: Withhold palbociclib; repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, re-start palbociclib at the same dose. • Day 8 and/or 15 of the first 3 cycles: Continue palbociclib at current dose and repeat complete blood count monitoring within 1 week. • Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles.
Grade 3 neutropenia with fever ≥38.3°C and/or infection	• Withhold palbociclib until recovery to Grade ≤2. • Resume at the next lower dose.
Grade 4 [a]	• Withhold palbociclib until recovery to Grade ≤2 • Resume at the next lower dose.

CTCAE = Common Terminology Criteria for Adverse Events.

[a] Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

Granulocyte-CSF may be used in the management of febrile neutropenia as clinically indicated.

CDK4/6 inhibitors, including palbociclib, may cause rare but severe inflammation of the lungs, resulting in serious cases including fatalities. All patients receiving palbociclib should be monitored for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea). In patients who have new or worsening respiratory

symptoms and are suspected to have developed ILD/pneumonitis, interrupt palbociclib immediately and evaluate the patient. Permanently discontinue palbociclib in patients with severe ILD/pneumonitis. See Table 8 for management pneumonitis management guidelines.

For all other non-hematologic toxicities assessed by the investigator as related to palbociclib, suggested guidelines for palbociclib dose modification are shown in Table 11 (see local prescribing information).

In general, the investigator may consider continuing palbociclib if the observed adverse event is not thought to be palbociclib-related. Palbociclib does not need to be interrupted for hyperglycemia; however, careful consideration should be given to toxicities known to be associated with palbociclib. Decisions on interruption of any of the study treatment components (inavolisib/placebo, palbociclib, fulvestrant) should be made independently of the others; i.e., one study treatment component alone may be interrupted for AE(s) associated with that medication without mandatory interruptions of the other study treatment components. For non-hematologic toxicities attributed to the combination of inavolisib, palbociclib and fulvestrant, it is preferred to initially dose-reduce one drug (i.e., inavolisib or palbociclib), then the other drug (e.g., if inavolisib dose was reduced but toxicity persisted, then reduce the dose of palbociclib), depending upon the nature and severity of the toxicity. However, if based on the investigator's judgment there is a concern for overlapping toxicity then the doses of both drugs may be reduced. Further dose de-escalation may be considered if the same toxicity recurs.

Table 11 Palbociclib Dose Modification and Management: Non-Hematologic Toxicities

CTCAE Grade	Dose Modification
Grade 1 or 2	• No dose adjustment is required.
Grade ≥ 3 [a]	• Withhold palbociclib until symptoms resolve to Grade ≤ 1 or Grade ≤ 2 (if not considered a safety risk for the patient). • Resume at the next lower dose. [b]

CTCAE = Common Terminology Criteria for Adverse Events

[a] If persisting despite optimal medical treatment.

[b] See the local prescribing information for recommended dose reductions.

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 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 a 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). All adverse events, including those that lead to dose modifications or study treatment discontinuation, should be carefully evaluated for medical significance.

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

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

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

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

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

- Grade ≥3 hyperglycemia
- Grade ≥3 rash
- Grade ≥3 diarrhea
- Grade ≥2 pneumonitis
- Grade ≥2 colitis or enterocolitis
- Grade ≥3 stomatitis or mucosal inflammation
- Grade ≥3 ALT or AST elevation

Adverse events of special interest for general drug development:

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an

infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events to Monitor

Additional data collection may occur for all grades of specific adverse events (e.g., pneumonitis, colitis/enterocolitis, rash, stomatitis, and ocular events) to enable a more detailed analysis of these events. The Sponsor may ask sites to send confirmatory data for adverse events (e.g., CT scans and reports for pneumonitis or colitis; biopsy reports for colitis, rash). The Sponsor may also ask sites to send tissue (e.g., biopsies from colitis or rash, if appropriate) and photographs (e.g., stomatitis, rash, or ocular events, if appropriate and with consent).

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 assess seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

Mobile nurses will be properly trained by the MN vendor on how to identify and record all adverse events in accordance with the instructions and within the protocol-mandated reporting period. The investigator must review and assess the adverse events prior to recording of the events in eCRF.

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 any study drug (i.e., 30 days after the final study treatment with inavolisib/placebo or palbociclib or fulvestrant, whichever is last), or until initiation of another anti-cancer therapy, whichever occurs first. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

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

Table 12 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 any event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also (Table 13):

- 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 13 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 individually assessed for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., 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 (Normal Range: 3.5–5.0 mEq/mL) 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, unless the known or suspected cause changes (see Section 5.3.5.4 for details on recording persistent adverse events); while recurrent clinically significant laboratory abnormalities should be entered as separate Adverse Events.

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF, unless the known or suspected cause changes (see Section 5.3.5.4 for details on recording persistent adverse events); while recurrent clinically significant vital sign abnormalities should be entered as separate Adverse Events.

5.3.5.6 Abnormal Liver Function Tests

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

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

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

5.3.5.7 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 independent monitoring committee 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"** may 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.

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event. Cases of clinical/symptomatic progression will not be considered as objective disease progression per RECIST v1.1, and should be reported only as a

reason for End of Treatment, when appropriate. The Overall Tumor Assessment at such a timepoint should be reported strictly per RECIST v1.1.

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., biopsy, for study drug administration, perform an efficacy measurement for the study)
- 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

The following hospitalization scenario is not considered to be a serious adverse event, but should be reported as an adverse event instead:

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

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

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

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

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm

- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, qualifies as an AESI or is a pregnancy, 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). For inavolisib/placebo, 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 inavolisib/placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

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

5.3.5.12 Patient-Reported Outcome Data

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

5.4 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 Emergency Medical Contacts

Telephone No.:	+44 1707 368309 (Welwyn Garden City, UK)
Mobile Telephone No.:	+44 (0) 7826066306 (Welwyn Garden City, UK)
Telephone No.:	+1 (650) 467-4557 (South San Francisco, CA, USA)
Mobile Telephone No.:	+1 (650) 438-8853 (South San Francisco, CA, USA)

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all 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, serious adverse events and adverse events of special interest will be reported until 30 days after the final dose of study drug, or until initiation of another anti-cancer therapy, whichever occurs first. 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 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 during the study or within 60 days after the final dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment 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 if their partner becomes pregnant during the study or within 98 days after the final dose of study drug. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form 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 pregnant partner and 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 should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

After the end of the adverse event reporting period (defined as 30 days after the final dose of study treatment), all deaths, regardless of cause or relatedness, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event 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 documents listed below:

Drug	Document
Inavolisib	Inavolisib Investigator's Brochure
Palbociclib	Palbociclib SmPC
Fulvestrant	Fulvestrant SmPC

SmPC = Summary of Product Characteristics.

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary efficacy objective for this study is to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of PFS. The primary efficacy analysis population will consist of all randomized patients grouped according to their assigned treatment at randomization based on IxRS.

The safety analysis population consists of all patients who received at least one dose of study drug and is based on the treatment the patients actually received, that is, all patients who received at least one dose of inavolisib are included in the inavolisib plus palbociclib and fulvestrant group and all patients who received at least one dose of palbociclib and/or fulvestrant (and no inavolisib) are included in the palbociclib and fulvestrant group.

The primary analysis is triggered by the number PFS events required to achieve *85*% power with 5% level of significance based on the assumptions outlined in Section 6.1. The *194* events are expected to have occurred *approximately 50* months after first patient randomized.

Method for type I error control of secondary endpoints, detailed list of planned sensitivity analyses and further additional information to the protocol are specified in the Statistical Analysis Plan (SAP). *The SAP may override the analyses as described in the study protocol, as applicable.* Details on the planned interim futility analysis and safety reviews are outlined in the iDMC charter.

6.1 DETERMINATION OF SAMPLE SIZE

Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- Two-sided log-rank test at the 0.05 level of significance
- 85% power to detect a hazard ratio for inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant of 0.65, corresponding to an improvement in median PFS from 11 to 16.9 months
- Exponential distribution of PFS
- An annual dropout rate of 15%

With these assumptions, 194 PFS events are required to achieve 85% power for the primary analysis. The 320 patients will be enrolled over approximately 43 months and the primary analysis is expected to occur $approximately\ 50$ months after the first patient randomized.

The minimal detectable difference for the PFS hazard ratio is 0.754 (i.e., an improvement $from$ 11 to 14.6 months in median PFS).

Of the 320 patients, no more than 60 patients will be allowed to have a *PIK3CA* tumor mutation not confirmed by the central $F1LCDx$ assay. As such, at least 260 patients will have the presence of (one or more) *PIK3CA* mutation(s) confirmed by the central $F1LCDx$ assay (see Appendix 10).

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature treatment and study discontinuation will be listed and summarized. Major protocol deviations, including violations of inclusion and/or exclusion criteria, will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including age, disease history, and stage at study entry) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment based on IxRS.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant 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), according to RECIST v1.1

Data for patients without the occurrence of disease progression or death will be censored at the time of the last tumor assessment (or at the time of randomization if no tumor assessment was performed after the baseline visit).

The primary efficacy analysis population will consist of all randomized patients grouped according to their assigned treatment at randomization.

The primary analysis of the study will test the equality of PFS distributions in the inavolisib plus palbociclib and fulvestrant and placebo plus palbociclib and fulvestrant arms, as follows:

> **H0**: PFS inavolisib plus palbociclib and fulvestrant = PFS placebo plus palbociclib and fulvestrant
>
> versus
>
> **H1**: PFS inavolisib plus palbociclib and fulvestrant $\neq$ PFS placebo plus palbociclib and fulvestrant

The treatment arms will be compared using a two-sided stratified log-rank test. The stratification factors that will be used are the same as those for randomization:

- Visceral disease (yes or no)
- Endocrine resistance
  (primary or secondary according to ESMO ABC4 guidelines [Cardoso et al. 2018])
- Geographic region (North American/Western Europe, Asia, or other)

The results from the unstratified log-rank test also will be provided.

Survival curves in each treatment arm will be estimated using Kaplan-Meier estimates. The Kaplan-Meier estimates will provide a visual description of the survival curves and the difference across treatment arms. In addition, the Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The treatment effect will be quantified via a hazard ratio, computed from a stratified Cox proportional-hazards regression, including a 95% CI.

Sensitivity analyses will be conducted including only patients whose tumor *PIK3CA* mutation status has been confirmed centrally in blood and based on independent central review of response. Further sensitivity analyses are defined in the SAP.

6.4.2 Secondary Efficacy Endpoints

*The t*ype I error–controlled secondary endpoint of this study is OS, objective response rate, BOR, CBR, TTD in pain, TTD in physical functioning (PF), TTD in role functioning (RF), and TTD in Global Health Status/Quality of Life (GHS/QoL). *OS will be formally tested only if PFS is statistically significant. For additional details, please refer to the SAP.* The primary efficacy analysis population is used for all secondary endpoints unless otherwise specified.

6.4.2.1 Overall Survival

Overall survival after randomization is defined as the time from randomization to death from any cause. 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 post-baseline information will be censored at the date of randomization.

Analysis methodology is as outlined for the primary endpoint, PFS.

An interim analysis of OS will be performed at the time of the primary analysis of PFS. In addition to the fixed sequence testing approach described before, a group-sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets 1983) for OS interim and final analyses, which will occur approximately 19 months later, as defined in Section 6.9.1.1.

The median OS in the control arm is assumed to be 35 months and the expected median OS in the experimental treatment arm is assumed to be 50 months, equating to a hazard ratio of 0.7. At the time of the primary PFS analysis, on the basis of the above assumptions, 105 OS events are expected to have occurred. 153 OS events are expected to have occurred at the final analysis, which will occur approximately 19 months later.

Of note, the endpoint of OS may not be met at the time of the *final* analysis because *the data may not be mature.* Therefore, additional *exploratory* analyses of OS *may be* conducted after the *final* analysis at timepoints defined through study milestones, such as Health Authority interactions. *Please refer to the SAP for further details.*

6.4.2.2 Objective Response Rate

Objective response rate is defined as the proportion of patients with a CR and/or PR on at least two consecutive occasions ≥4 weeks apart, according to RECIST v1.1. Patients who did not achieve a confirmed response and patients with no response assessments (for whatever reason) will be considered non-responders.

An estimate of the response rate and its 95% CI will be calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms will be compared using the stratified Mantel-Haenszel test. Confidence intervals for the difference in objective response rates between the two arms will be determined using the normal approximation to the binomial distribution.

6.4.2.3 Best Overall Response Rate

Best overall response rate is defined as the proportion of patients with a CR or PR, as determined according to RECIST v1.1. Patients who did not achieve a CR or PR and patients with no response assessments (for whatever reason) will be considered non-responders.

Analysis methodology is as outlined for objective response rate.

6.4.2.4 Clinical Benefit Rate

Clinical benefit rate is defined as the proportion of patients with a CR, PR, and/or SD for at least 24 weeks, as determined according to RECIST v1.1. Patients who did not achieve clinical benefit and patients with no response assessments (for whatever reason) will be considered non-responders.

Analysis methodology is as outlined for objective response rate.

6.4.2.5 Duration of Objective Response

The analysis of DOR will include only patients who achieved an objective response to study treatment. DOR is defined as the time from the first occurrence of a PR or CR to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined according to RECIST v1.1. Data for patients without the occurrence of disease progression or death will be censored at the time of the last tumor assessment.

Analysis methodology is as outlined for the primary endpoint, PFS. Comparisons between treatment arms using stratified and unstratified log rank test will be made for descriptive purposes. Because the determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing will not be performed.

6.4.2.6 Patient- Reported Outcomes (TTD of Pain, PF, RF, and GHS/QoL)

To evaluate TTD in pain, the “worst pain” item from the BPI-SF will be assessed. TTD is defined as the time from randomization to the first documentation of a 2-point increase from baseline in “worst pain.” A 2-point change is defined as clinically meaningful (Mathias et al. 2010). Patients who do not have an observed deterioration at the time of the clinical data cutoff will be censored at the last non-missing assessment date. Patients without a post-baseline assessment will be censored at the time of randomization.

Time to deterioration in PF, RF, and GHS/ QoL will be assessed. TTD is defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the specific scale:

- Physical Function (items 1 through 5)
- Role Function (items 6 and 7)
- Global Health Status (GHS)/Quality of Life (QoL) (items 29 and 30)

Patients who do not have an observed deterioration at the time of the clinical data cutoff will be censored at the last non-missing assessment date. Patients without a post-baseline assessment will be censored at the time of randomization.

A ≥10-point change is defined as a clinically meaningful difference (Osoba et al. 1998) on all scales of the EORTC-QLQ-C30.

6.4.3 Exploratory Efficacy Endpoints

6.4.3.1 Exploratory Clinical Outcomes

- Time to end of next-line treatment (proxy for time to second objective disease progression [PFS2]), defined as the time from randomization to end or discontinuation of next-line treatment, or death from any cause (whichever occurs first). Data for patients without the occurrence of second objective disease progression or death and patients who have not started next-line treatment will be censored at the last date they were known to be alive. Data from patients without post-baseline information will be censored at the date of randomization. Analysis methodology is as outlined for the primary endpoint, PFS.
- Time to first SRE, defined as the time from randomization to the first occurrence of an SRE. An SRE is a pathologic fracture, radiation therapy to bone, cancer-related surgery to bone, or spinal cord compression. Data from patients without the occurrence of an SRE will be censored at the last valid visit. Data from patients without post-baseline information will be censored at the date of randomization. Analysis methodology is as outlined for the primary endpoint, PFS.

6.4.3.2 Exploratory Patient Reported-Outcome Analyses

Summary statistics (mean, SD, 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 EORTC QLQ-C30 and BR23 questionnaire for each assessment timepoint. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be reported independently 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).

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

6.5 SAFETY ANALYSES

The safety analysis population consists of all patients who received at least one dose of study drug and is based on the treatment the patients actually received; that is, all patients who received at least one dose of inavolisib are included in the inavolisib plus palbociclib and fulvestrant group and all patients who received at least one dose of palbociclib and/or fulvestrant (and no inavolisib) are included in the palbociclib and fulvestrant group.

The safety objective for this study is to evaluate the safety of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

The exploratory safety objective for this study is to evaluate tolerability of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant from the patient's perspective, on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities as assessed through use of the NCI PRO-CTCAE and the “bother from side effects” item
- Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE and the “bother from side effects” item

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) and dose intensity will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse

events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

6.5.1 Exploratory Analyses of PRO-CTCAE Data

Patient-Reported Outcome-Common Terminology Criteria for Adverse Events 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, interference) will be summarized at each assessment timepoint by treatment arm. For items that are rated on a 5-point Likert scale, the maximum post-baseline score and change from baseline will be summarized by treatment arm.

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

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients who received at least one dose of study drug and is based on the treatment patients actually received; that is, all patients who received at least one dose of inavolisib are included in the inavolisib plus palbociclib and fulvestrant group and all patients who received at least one dose of palbociclib and/or fulvestrant (and no inavolisib) are included in the palbociclib and fulvestrant group.

Individual and mean plasma concentration of inavolisib, palbociclib, and fulvestrant versus time data will be tabulated and plotted. Inavolisib plasma concentration versus time data, together with information on dosing and patient characteristics, will be pooled and analyzed using a population PK (PopPK) analysis approach, as appropriate. Non-linear mixed-effect modeling will be used for the estimation of PopPK parameters for inavolisib. Covariates such as patient demographics (e.g., age, sex, body size) may be tested for significance on PK parameters of interest.

The PK data may be combined with the safety, efficacy, and biomarker data for exposure-response modeling as an exploratory objective. PK and PK/pharmacodynamics analyses may be reported in separate standalone reports. Additional PK analyses will be conducted as appropriate.

6.7 EXPLORATORY 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 to understand the association of these markers with study treatment response. Results will be presented in a separate report.

6.8 HEALTH STATUS UTILITY ANALYSES

The EQ-5D-5L will be scored according to its manual (van Reenen and Janssen. 2015) (see Appendix 8). Absolute score and change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at over time.

6.9 INTERIM ANALYSIS

6.9.1 Planned Interim Analysis

An iDMC will convene to review cumulative safety data approximately every 4 months (see Section 3.1.2).

One interim analysis for futility will be conducted after approximately 75 PFS events (33% of information) are observed. The futility boundary is non-binding. The cutoff is expected to occur 18 months after first patient enrolled and, hence, approximately 265 patients will have been enrolled when the decision is available.

As an additional safety monitoring measure, an interim safety review will be performed after the enrollment of the first 25 patients and treatment for at least three cycles.

One interim analysis will be performed for OS at the time of the primary endpoint analysis.

6.9.1.1 *Alpha-Spending Function for OS Analysis*

The type I error probability will be controlled by using a Lan-DeMets (O'Brien Fleming) a-spending function for the secondary endpoint, OS, at a 5% overall level of significance. The stopping boundaries to be used for the efficacy test will be calculated using the a-spending function approach described by Lan and DeMets (1983). This function generates stopping boundaries that closely resemble the O'Brien-Fleming boundaries (O'Brien and Fleming 1979) (see Table 14).

Table 14 Stopping Boundaries for Efficacy at the Interim or Final OS Analysis

Look	*p-Value Stopping Boundary (Effect Scale)*	*Information Fraction*
First interim analysis	*0.0132 (or hazard ratio 0.615)*	*68% (105/153)*
Final analysis 19 months later	*0.0460 (or hazard ratio 0.724)*	*100% (153/153)*

The actual boundaries will be calculated at the time of OS analysis based on the observed information fraction (i.e. actual number of events observed at time of analysis over the total planned target number of events). For further details, refer to the SAP.

6.10 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and data from other external vendors such as analytical labs 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.

Patient-reported outcome data will be collected through the use of an electronic device provided by a vendor (see Section 6.12 for details).

6.11 ELECTRONIC CASE REPORT FORMS

Electronic case report forms 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.

6.12 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 FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a 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.

6.13 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 6.15.

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.

6.14 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.

6.15 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of study drugs, including eCRFs, electronic PRO data, 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.

7. ETHICAL CONSIDERATIONS

7.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the 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.

7.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation to 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.

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy). For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in

each patient's study file or in the site file and must be available for verification by study monitors at any time.

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

7.3 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 8.7).

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.

7.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from FMI or the alternative, Sponsor-designated central testing laboratory where applicable). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy *in the* study data publication (see Section 8.6).

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 8.6).

7.5 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 3.1.2).

8. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

8.1 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.

8.2 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.

8.3 SITE INSPECTIONS

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

8.4 MANAGEMENT OF STUDY QUALITY

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

8.5 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 200 sites globally will participate to enroll approximately 320 patients. Enrollment and randomization to treatment arms will occur through an IxRS, which will also be utilized to manage site drug supply.

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

An iDMC will be utilized to monitor and evaluate patient safety throughout the study. The procedures describing the conduct of, and communication with, the iDMC will be described in a separate Charter.

8.6 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 7.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical 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.

8.7 PROTOCOL AMENDMENTS

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

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

9. REFERENCES

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

Acconcia F, Totta P, Ogawa S, et al. Survival versus apoptotic 17beta-estradiol effect: role of ER alpha- and ER beta−activated non-genomic signaling. J Cell Physiol 2005;203:193−201.

American Cancer Society. Key Statistics for Breast Cancer in Men [resource on the Internet]. 2019 [cited: 8 August 2019]. Available from: https://www.cancer.org/cancer/breast-cancer-in-men/about/key-statistics.html

André F, Ciruelos F, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. N Engl J Med 2019;380:1929–40.

Aoki M, Batista O, Bellacosa A, et al. The AKT kinase: molecular determinants of oncogenicity. Proc Natl Acad Sci USA 1998;95:14950–5.

Atkinson TM, Li Y, Coffey CW, et al. Reliability of adverse symptom event reporting by clinicians. Qual Life Res 2012;21:1159–64.

Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J Clin Oncol 2012;30:2718–24.

Bachman KE, Argani P, Samuels Y, et al. The PIK3CA gene is mutated with high frequency in human breast cancers. Cancer Biol Ther 2004;3:772–5.

Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med 2010;362:865–9.

Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014;106:1–11.

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

Bellacosa A, de Feo D, Godwin AK, et al. Molecular alterations of the AKT2 oncogene in ovarian and breast carcinomas. Int J Cancer 1995;64:280–5.

Bengtsson T, Sanabria-Bohorquez SM, McCarthy TJ, et al. Statistically assigned response criteria in solid tumors (STARCIST). Cancer Imaging 2015;15:9.

Björnström L, Sjöberg M. Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. Mol Endocrinol 2005;19:833−42.

Boulay A, Rudloff J, Ye J, et al. Dual inhibition of mTOR and estrogen receptor signaling in vitro induces cell death in models of breast cancer. Clin Cancer Res 2005;11:5319–28.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Caldas CM. Genomic stratification of breast cancer and its implications. Presented at the Annual Meeting of the American Association for Cancer Research; Cambridge, United Kingdom; 19 April 2016.

Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70.

Cantrell DA. Phosphoinositide 3-kinase signaling patyways. J Cell Sci 2001; 114:1439−45.

Cardoso F, Senkus E, Costa A, et al. 4th ESO−ESMO international consensus guidelines for advanced breast cancer. Ann Oncol 2018;29:1634–57.

Cheng JQ, Godwin A, Bellacosa A, et al. AKT2, a putative oncogene encoding a member of a subfamily of protein-serine/threonine kinases, is amplified in human ovarian carcinomas. Proc Natl Acad Sci USA 1992;89:9267–71.

Clark TA, Chung JH, Kennedy M, et al. Analytical Validation of a Hybrid Capture-Based Next-Generation Sequencing Clinical Assay for Genomic Profiling of Cell-Free Circulating Tumor DNA. J Mol Diagn 2018;20:686–702.

Cleeland C. The Brief Pain Inventory User Guide. MD Anderson Cancer Center. 2009.

Creighton CJ, Fu X, Hennessy FT, et al. Proteomic and transcriptomic profiling reveals a link between the PI3K pathway and lower estrogen-receptor (ER) levels and activity in ER+ breast cancer. Breast Cancer Res 2010;12:R40.

Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425–39.

Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 2012;486:346.

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

Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol 2010;28:4594–4600.

Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet 2006;7:606–19.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer 2001;37:1331–4.

Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2−negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25–35.

Finn RS, Martin M, Rugo HS, et al. PALOMA-2: Primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal women with ER+/HER2− advanced breast cancer (ABC). J Clin Oncol 2016;34:S507.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Foukas LC, Claret M, Pearce W, et al. Critical role for the p110alpha phosphoinositide-3-OH kinase in growth and metabolic regulation. Nature 2006;441:366–70.

Fromme EK, Eilers KM, Mori M, et al. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol 2004;22:348–90.

Geuna E, Roda D, Rafii S, et al. Complications of hyperglycaemia with PI3K-AKT-mTOR inhibitors in patients with advanced solid tumours on Phase I clinical trials. Br J Cancer 2015;113:1541–47.

Gustin JP, Cosgrove DP, Park BH. The PIK3CA gene as a mutated target for cancer therapy. Curr Cancer Drug Targets 2008;8:733–40.

Gutierrez MC, Detre S, Johnston S, et al. Molecular changes in tamoxifen-resistant breast cancer: relationship between estrogen receptor, HER2, and p38 mitogen activated protein kinase. J Clin Oncol 2005;23:2469−76.

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646−74.

Harbeck N, Iyer S, Turner N, et al. Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient reported outcomes from the PALOMA-3 trial. Ann Oncol 2016;27:1047–54.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Herrera-Abreu MT, Palafox M, Asghar U, et al. Early adaptation and acquired resistance to CDK4/6 inhibition in estrogen receptor–positive breast cancer. Cancer Res 2016;76:2301–13.

Howell A, Robertson JF, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 2002;20:3396–3403.

Irvin W Jr, Muss HB, Mayer DK, et al. Symptom management in metastatic breast cancer. Oncologist 2011;16:1203–14.

Janku F, Juric D, Cortes J, et al. Phase I study of the PI3Ka inhibitor alpelisib (BYL719) plus fulvestrant in patients with PIK3CA-altered and PIK3CA-wild-type, ER+/HER2–, locally advanced or metastatic breast cancer. San Antonio Breast Cancer Symposium, 2014.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Johnston SRD. Enhancing the efficacy of hormonal agents with selected targeted agents. Clin Breast Cancer 2009;9:S28–36.

Juric D, Burris H, Schuler M, et al. Phase I study of the PI3Kα inhibitor BYL719, as a single agent in patients with advanced solid tumors (aST). Ann Oncol 2014;25(suppl 4):iv146–iv164.

Kirkegaard T, Witton CJ, McGlynn LM, et al. AKT activation predicts outcome in breast cancer patients treated with tamoxifen. J Pathol 2005;207:139–46.

Kodahl AR, Ehmsen S, Pallisgaard N, et al. Correlation between circulating cell-free PIK3CA tumor DNA levels and treatment response in patients with PIK3CA-mutated metastatic breast cancer. Mol Oncol 2018;12:925–35.

Lan KKG, DeMets DL. Discrete Sequential Boundaries for Clinical Trials. Biometrika. 1983;70:659.

Li J, Yen C, Liaw D, et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 1997;275:1943–7.

Luo J, Sobkiw CL, Hirshman MF, et al. Loss of class IA PI3K signaling in muscle leads to impaired muscle growth, insulin response, and hyperlipidemia. Cell Metab 2006:355–66.

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

Mathias SD, Crosby RD, Qian Y, et al. Estimating minimally important differences (MID) for the worst pain rating of the brief pain inventory (BPI)-short form (SF). J Clin Oncol 2010;28(15_suppl): 6112.

Mayer IA, Prat A, Egle D, et al. A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB). Clin Cancer Res. 2019 May 15;25(10):2975-2987. doi: 10.1158/1078-0432.CCR-18-3160. Epub 2019 Feb 5.

Miller TW, Pérez-Torres M, Narasanna A, et al. Loss of phosphatase and tensin homologue deleted on Chromosome 10 engages ErbB3 and insulin-like growth factor-I receptor signaling to promote antiestrogen resistance in breast cancer. Cancer Res 2009;69:4192–201.

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

Miron A, Varadi M, Carrasco D, et al. PIK3CA mutations in in situ and invasive breast carcinomas. Cancer Res 2010;70:5674–8.

Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer 2009;9:631–43.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Breast cancer [resource on the Internet]. 2019 Mar 14. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

O'Brien C, Wallin JJ, Sampath D, et al. Predictive biomarkers of sensitivity to the phosphatidylinositol 3′ -kinase inhibitor GDC-0941 in breast cancer preclinical models. Clin Cancer Res 2010;16:3670–83.

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

Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med 2011;62:233–47.

Pakhomov SV, Jacobsen SJ, Chute CG, et al. Agreement between patient-reported symptoms and their documentation in the medical record. Am J Manag Care 2008;14:530–9.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44.

Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. J Natl Cancer Inst 2011;103:185–8.

Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet 2016;388:2997–3005.

Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol 2017;18:654–62.

Rugo HS, Diéras V, Gelmon KA, et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. Ann Oncol 2018;29:88–94.

Saal LH, Holm K, Maurer M, et al. PIK3CA mutations correlate with hormone receptors, node metastasis, ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. Cancer Res 2005;65:2554–9.

Sabnis G, Goloubeva O, Jelovac D, et al. Inhibition of the phosphatidylinositol 3 kinase/Akt pathway improves response of long-term estrogen-deprived breast cancer xenografts to antiestrogens. Clin Cancer Res 2007;13:2751–7.

Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001;414:799–806.

Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. Science 2004;304:554.

Schleifman EB, Desai R, Spoerke JM, et al. Targeted biomarker profiling of matched primary and metastatic estrogen receptor positive breast cancers. PLoS One 2014;9:e88401.

Shi Q, Wang XS, Mendoza TR, et al. Assessing persistent cancer pain: a comparison of current pain ratings and pain recalled from the past week. J Pain Symptom Manage 2009;37:168–74.

Shoman N, Klassen S, McFadden A, et al. Reduced PTEN expression predicts relapse in patients with breast carcinoma treated by tamoxifen. Mod Pathol 2005;18:250–9.

Shou J, Massarweh S, Osborne, CK, et al. Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. J Natl Cancer Ins. 2004;96:926–35.

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

Staal SP. Molecular cloning of the AKT oncogene and its human homologues AKT1 and AKT2: amplification of AKT1 in a primary human gastric adenocarcinoma. Proc Natl Acad Sci USA 1987;84:5034–7.

Steck PA, Pershouse MA, Jasser SA, et al. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 1997;15:356–62.

Stemke-Hale K, Gonzalez-Angulo AM, Lluch A, et al. An integrative genomic and proteomic analysis of PIK3CA, PTEN, and AKT mutations in breast cancer. Cancer Res 2008;68:6084–91.

Tabernero J, Rojo F, Calvo E, et al. Dose-and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: A phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol 2008;26:1603–10.

Trotti A, Pajak TF, Gwede CK, et al. TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. Lancet Oncol 2007;8:613–24.

Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med 2015;373:209–19.

Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med 2018;379:1926–36.

U.S. Food and Drug Administration. Guidance for industry. In vitro metabolism- and transporter-mediated drug-drug interaction studies [resource on the Internet]. 2017. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-metabolism-and-transporter-mediated-drug-drug-interaction-studies-guidance-industry.

van Reenen M and Janssen B. EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument Version 2.1. EuroQoL. April 2015.

Vanhaesebroeck B, Stephens L, Hawkins P. PI3K signalling: the path to discovery and understanding. Nat Rev Mol Cell Biol 2012;13:195–203.

Verma S, DeMichele AM M, Loi S, et al. Updated safety from a double-blind phase 3 trial (PALOMA-3) of fulvestrant with placebo or with palbociclib in pre- and postmenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy. Proceedings of the San Antonio Breast Cancer Symposium: 2015 Dec 8–12.

Vora SR, Juric D, Kim N, et al. CDK 4/6 inhibitors sensitize PIK3CA mutant breast cancer to PI3K inhibitors. Cancer Cell 2014;26:136–49.

Wood R, de Courcy J, Mitra D, et al. Patient reported pain severity and interference in HR+/HER2− advanced/metastatic breast cancer in real world settings. Annals of Oncology 2016;27:284P.

Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 2013;30:870–84.

Appendix 1
Schedule of Activities

Assessment	Screen [a]	Treatment Period								Post-Treatment F/U			Survival F/U [f]
		Cycle 1					Cycle 2 and Beyond		TX Discon [b]	30-Day Safety F/U [c]	Hyper-glycemia F/U [d]	Tumor Assess. F/U with PRO [e]	
Day (Window)	– 28 to – 1	1	4 (± 1)	8 (± 1)	15 (± 1)	22 (± 1)	1 (± 2)	15 (± 2)	≤ 30 days from last dose	30 (± 7 days) from last dose	Monthly up to 3 months	Q8W first 2 yrs; Q12W thereafter	Every 3 months
Informed consent [g]	x												
Demographic data	x												
Medical history and baseline conditions	x												
Vital signs [h]	x	x	x	x	x	x	x	C2 & C3 only	x				
Weight [h]	x	x		x	x		x	C2 & C3 only	x				
Height [h]	x												
Complete physical examination [i]	x	x							x				
Limited physical examination [j]			x	x	x	x	x	C2 & C3 only					
ECOG PS	x	x		x	x		x	C2 & C3 only	x				
Ophthalmic examination [k]	x						C6 only		x				

Appendix 1: Schedule of Activities

Assessment	Screen [a]	Treatment Period								Post-Treatment F/U			
		Cycle 1					Cycle 2 and Beyond		TX Discon [b]	30-Day Safety F/U [c]	Hyper-glycemia F/U [d]	Tumor Assess. F/U with PRO [e]	Survival F/U [f]
Day (Window)	– 28 to – 1	1	4 (± 1)	8 (± 1)	15 (± 1)	22 (± 1)	1 (± 2)	15 (± 2)	≤ 30 days from last dose	30 (± 7 days) from last dose	Monthly up to 3 months	Q8W first 2 yrs; Q12W thereafter	Every 3 months
12-lead ECG [l]	x	x					x		x				
Hematology [m]	x	x	x	x	x	x	x	C2 & C3 only	x				
Fasting serum or plasma chemistry [n]	x	x	x	x	x	x	x	C2 & C3 only	x				
FSH and plasma estradiol [o]	x												
Serum or urine pregnancy test [p]	x	x					x		x				
Urinalysis [q]	x	x	x				x		x				
Glycosylated hemoglobin (HbA1c) [r]	x						Every 3 cycles starting on C3D1		x		x		
Fasting glucose [s]	x	x	x	x	x	x	x	C2 & C3 only	x		x		
Fasting insulin [s]	x	x					x		x		x		

Appendix 1: Schedule of Activities

Assessment	Screen [a]	Treatment Period								Post-Treatment F/U			
		Cycle 1					Cycle 2 and Beyond		TX Discon [b]	30-Day Safety F/U [c]	Hyper-glycemia F/U [d]	Tumor Assess. F/U with PRO [e]	Survival F/U [f]
Day (Window)	– 28 to – 1	1	4 (± 1)	8 (± 1)	15 (± 1)	22 (± 1)	1 (± 2)	15 (± 2)	≤ 30 days from last dose	30 (± 7 days) from last dose	Monthly up to 3 months	Q8W first 2 yrs; Q12W thereafter	Every 3 months
Fasting lipid profile plus amylase, and lipase [t]	x						Every 3 cycles starting on C3D1		x				
Serum fibrinogen, coagulation (INR, aPTT, PT)	x	x					x		x				
Plasma PK sample		Refer to *Appendix 2*											
Tumor assessment [u]	x	Every 8 weeks during the first 2 years, every 12 weeks thereafter							x			x	
Bone scan	x												
Pre-treatment tumor tissue sample (fresh or archival) for biomarkers [v]	x												
Fresh tumor tissue on-treatment biopsy sample (optional) [w]					x								

Appendix 1: Schedule of Activities

Assessment	Screen [a]	Treatment Period								Post-Treatment F/U			
		Cycle 1					Cycle 2 and Beyond		TX Discon [b]	30-Day Safety F/U [c]	Hyper-glycemia F/U [d]	Tumor Assess. F/U with PRO [e]	Survival F/U [f]
Day (Window)	– 28 to – 1	1	4 (± 1)	8 (± 1)	15 (± 1)	22 (± 1)	1 (± 2)	15 (± 2)	≤ 30 days from last dose	30 (± 7 days) from last dose	Monthly up to 3 months	Q8W first 2 yrs; Q12W thereafter	Every 3 months
Fresh tumor tissue progression biopsy sample (optional) [w]									At time of disease progress.				
Blood sample for ctDNA [x]	x												
Plasma sample for somatic mutation determination [y]		x			x		C2, then every 3 cycles thereafter starting on C3D1 (i.e., Cycles 3, 6, 9, etc.)		x				
Blood sample for biomarker NGS [z]		x											
Blood sample for WGS [aa]		x											
Inavolisib/placebo administration [bb]		x	x	x	x	x	x	C2 & C3 only					

Appendix 1: Schedule of Activities

Assessment	Screen [a]	Treatment Period								Post-Treatment F/U			
		Cycle 1					Cycle 2 and Beyond		TX Discon [b]	30-Day Safety F/U [c]	Hyper-glycemia F/U [d]	Tumor Assess. F/U with PRO [e]	Survival F/U [f]
Day (Window)	– 28 to – 1	1	4 (± 1)	8 (± 1)	15 (± 1)	22 (± 1)	1 (± 2)	15 (± 2)	≤ 30 days from last dose	30 (± 7 days) from last dose	Monthly up to 3 months	Q8W first 2 yrs; Q12W thereafter	Every 3 months
Palbociclib administration [cc]		x	x	x	x		x	C2 & C3 only					
Fulvestrant administration [dd]		x			x		x see footnote "dd"						
Concomitant medications [ee]	x	x	x	x	x	x	x	C2 & C3 only	x	x			
LHRH agonist [ff]	x						Monitor every 3 cycles [ff]						
Adverse events [gg]	x	x	x	x	x	x	x	C2 & C3 only	x	x			
Post-treatment assess. of ongoing hyperglycemia and management											x		
EORTC QLQ-C30, BPI-SF "worst pain" item, and EQ-5D-5L [hh]		x					x		x	x		x	x

Appendix 1: Schedule of Activities

Assessment	Screen [a]	Treatment Period								Post-Treatment F/U			
		Cycle 1					Cycle 2 and Beyond		TX Discon [b]	30-Day Safety F/U [c]	Hyper-glycemia F/U [d]	Tumor Assess. F/U with PRO [e]	Survival F/U [f]
Day (Window)	– 28 to – 1	1	4 (± 1)	8 (± 1)	15 (± 1)	22 (± 1)	1 (± 2)	15 (± 2)	≤ 30 days from last dose	30 (± 7 days) from last dose	Monthly up to 3 months	Q8W first 2 yrs; Q12W thereafter	Every 3 months
EORTC BR23 [hh]		x					x		x	x		x	x
NCI PRO-CTCAE [hh]		x			x		x	C2 & C3 only	x	x		x	x
Mid-cycle telephone call visit [ii]								C4 and beyond					
Post-treatment anti-cancer therapy [jj]										x	x	x	x
Survival [kk]													x

Appendix 1: Schedule of Activities

Assess. = assessment; BPI-SF = Brief Pain Inventory- Short Form; C = cycle; C1D1 = Cycle 1, Day 1; CT = computed tomography; ctDNA = circulating tumor DNA; Discon = discontinuation; eCRF = electronic Case Report Form; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire; EORTC BR23 = European Organisation for Research and Treatment of Cancer Breast Cancer 23 item Questionnaire; EQ-5D-5L = European Quality of Life 5-Dimension, 5-Level questionnaire; F/U = follow-up; FMI = Foundation Medicine Inc.; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; IM = intramuscular; INR = international normalized ratio; LDL = low-density lipoprotein; LHRH = luteinizing hormone–releasing hormone; MN = mobile nursing; MRI = magnetic resonance imaging; NCI = National Cancer Institute; NGS = next-generation sequencing; PK = pharmacokinetic; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; PO = by mouth; progress. = progression; PTT = partial thromboplastin time; Q8W = every 8 weeks; Q12W = every 12 weeks ;QD = once a day; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TX = treatment; WGS = whole genome sequencing; yrs = years.

Notes: The study consists of a screening period of up to 28 days, a treatment period, a post-treatment follow-up period (which includes a “30-day safety follow-up” for all patients, and when applicable, a “post-treatment hyperglycemia follow-up”, and/or a “post-treatment tumor assessment follow-up with PRO collection”), and a survival follow-up period. In the absence of unacceptable toxicities or unequivocal disease progression as determined by the investigator, patients may continue treatment with inavolisib/placebo plus palbociclib and fulvestrant until the end of the study. All assessments should be performed within 2 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Additional assessments may also be done at unplanned visits if clinically indicated. The investigator should review local laboratory results, including CBC, chemistry panel, and glucose, prior to study treatment administration.

Appendix 1: Schedule of Activities

For patients at participating sites who have provided written informed consent to participate in mobile nursing (MN) visits, the assessments or procedures shaded in gray in the table above may be performed by a trained mobile nurse at the patient's home.

[a] SCREENING PERIOD - Perform within 28 days prior to Cycle 1, Day 1, with the exception of laboratory assessments, which must be obtained within 14 days prior to Cycle 1, Day 1. Written informed consent is required before performing any study-specific tests or procedures and may be obtained at any time prior to such tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening. Unless otherwise stated, screening assessments that are done within 2 days prior to Cycle 1, Day 1 do not need to be repeated on Cycle 1, Day 1. Please note, a prescreening ICF may be signed and blood sample submitted for PIK3CA mutation assessment by the central F1Liquid assay before other screening procedures initiated.

[b] TREATMENT DISCONTINUATION VISIT - Patients who discontinue study treatment permanently will return to the clinic for a treatment discontinuation visit within 30 days after their final dose of study drug (inavolisib/placebo, palbociclib, or fulvestrant, whichever is discontinued last). The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] 30-DAY SAFETY FOLLOW-UP - Following study treatment discontinuation, all patients will be followed for safety for 30 days after final study treatment (including a 30-day follow-up clinic visit), or until the initiation of another anti-cancer therapy, whichever occurs first.

[d] POST-TREATMENT HYPERGLYCEMIA FOLLOW-UP - Patients on anti-hyperglycemic agents for the treatment of hyperglycemia during the study treatment and those patients with events of hyperglycemia ongoing at the end of the 30-day safety follow-up, will undergo additional safety follow-up assessments monthly until resolution of their fasting glucose to baseline levels, complete down-titration of their anti-hyperglycemic medications, or up to approximately 3 months after the final dose of study treatment, even if the patient initiates another anti-cancer therapy subsequent to study treatment discontinuation.

[e] POST-TREATMENT TUMOR ASSESSMENT FOLLOW-UP WITH PRO COLLECTION - Patients who discontinue active study treatment for reasons other than progression of disease or death will continue to have tumor assessments performed every 8 weeks ($\pm$ 7 days) for the first 2 years from randomization and every 12 weeks ($\pm$ 7 days) thereafter, and complete PRO assessments at those timepoints until documented disease progression or the initiation of another anti-cancer therapy, whichever occurs first.

[f] SURVIVAL FOLLOW-UP PERIOD - After study treatment discontinuation and post-treatment follow-up, all patients will be followed for survival and all subsequent anti-cancer therapies. These data will be collected approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

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

[h] VITAL SIGNS - Includes height, weight, respiratory rate, pulse rate, blood oxygenation (pulse oximetry), and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[i] COMPLETE PHYSICAL EXAMINATION - Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[j] LIMITED PHYSICAL EXAMINATION - Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated.

[k] OPHTHALMIC EXAMINATION - Patients will undergo ophthalmic examinations at baseline during the screening period, at Cycle 6 (± 2 weeks) during the study treatment period, at study treatment discontinuation, and based on any ocular disturbances. The ophthalmic examination should consist of a full ophthalmic exam with dilation and refraction with specific attention paid to lens examination and detailed documentation. In addition, patients will be asked if they have experienced any significant visual changes, pain, or sensitivity to light at each clinic visit. Any new eye-related symptoms including significant change in vision, eye pain, or photophobia will be evaluated by an ophthalmologist. All clinically significant findings must be reported as adverse events.

[l] ECG - Triplicate 12-lead ECG recordings will be obtained at baseline to determine eligibility; otherwise, single 12-lead ECG recordings will be performed.

[m] HEMATOLOGY- Hematology panel includes: RBC count, hemoglobin, hematocrit, reticulocyte count, platelet count, WBC count with differential count (neutrophils, bands [optional], eosinophils, basophils, monocytes, lymphocytes, other cells; i.e., must be sufficient for the determination of ANCs, lymphocytes). Laboratory samples should be drawn within 24 hours (all Cycle 1 and Cycle 2 visits) or within 48 hours prior to study drug administration at the clinic; results should be available to assess prior to dosing.

[n] FASTING CHEMISTRY - Fasting (≥ 8-hour fast) blood chemistry panel (serum or plasma) includes: sodium, potassium, chloride, bicarbonate (or total carbon dioxide if considered standard-of-care for the region), BUN or urea, creatinine, glucose, calcium, magnesium, phosphate, total protein, albumin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), total and direct bilirubin, and alkaline phosphatase (ALP). Laboratory samples should be drawn within 24 hours (all Cycle 1 and Cycle 2 visits) or within 48 hours prior to study drug administration at the clinic; results for glucose, bilirubin, ALP, AST, and ALT should be available prior to dosing.

[o] FSH AND PLASMA ESTRADIOL – For women not definitively confirmed as post-menopausal, FSH and plasma estradiol levels testing are required during screening to establish menopausal status. For some localities, estradiol levels may also be determined from serum.

[p] PREGNANCY TEST - Women of childbearing potential must have a negative serum pregnancy test result within 14 days of first dose of study treatment and serum or urine pregnancy tests will be performed on Day 1 of Cycles ≥ 2 and at study treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.

[q] URINALYSIS - Urinalysis (dipstick allowed) includes pH, specific gravity, glucose, protein, ketones, and blood; if clinically indicated, microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria.

[r] HbA1c - Assess at screening, every 3 cycles starting on Day 1 of Cycle 3 (e.g., Day 1 of Cycles 1, 3, 6, etc.), at treatment discontinuation visit, and monthly during the hyperglycemia safety follow-up.

[s] FASTING GLUCOSE AND INSULIN - Fasting (≥ 8-hour fast) insulin and glucose sample. Glucose levels may be obtained by glucometer (fingerstick). Samples should be drawn within 24 hours (all Cycle 1 and Cycle 2 visits) or within 48 hours prior to study drug administration at the clinic; glucose results must be available and reviewed prior to dosing. In addition, patients may be instructed to monitor fasting glucose more frequently via use of home glucometer.

[t] FASTING LIPID PROFILE PLUS AMYLASE AND LIPASE - Fasting (≥ 8-hour fast) lipid profile (includes total cholesterol, HDL, LDL, and triglycerides), amylase and lipase will be assessed at screening, every 3 cycles (e.g., Day 1 of Cycles 3, 6, etc.), and at treatment discontinuation visit.

[u] TUMOR ASSESSMENT - Tumor assessments are performed according to RECIST v1.1. Post-baseline tumor assessments should be performed every 8 weeks (± 7 days) from Cycle 1, Day 1 during the first 2 years, and every 12 weeks (± 7 days) thereafter, regardless of dose delay, treatment interruption or early treatment discontinuation, and until disease progression. At screening, bone scans or other institutional standard bone imaging should be acquired in all patients. The method used for a patient (CT or MRI scan or photographic measurements) must be the same throughout the study. A missed tumor assessment should be rescheduled as soon as possible. Patients who discontinue study treatment for reasons other than disease progression or death will continue onto the "post-treatment tumor assessment follow-up with PRO collection" (refer to footnote "hh").

[v] PRE-TREATMENT TUMOR TISSUE SAMPLE (FRESH OR ARCHIVAL) FOR BIOMARKERS - Pre-treatment tumor tissue samples for biomarkers are mandatory and are to be collected fresh (preferred) within the study screening period or a recent archival tumor tissue sample can be submitted. If only an archival tumor tissue sample is available, the sample should preferably be from the patient's metastatic disease. If none of these options are possible, please contact the Sponsor.

[w] FRESH TUMOR TISSUE BIOPSY SAMPLE (OPTIONAL) - Patients may consent for fresh biopsies to be collected during treatment and/or at the time of disease progression. Optional on-treatment fresh biopsies are to be performed between Days 15 and 22 of Cycle 1, approximately 1–4 hours post-dose. If possible, optional fresh biopsies at the time of disease progression should be obtained within 48 hours of the patient's final dose of study treatment, but no later than initiation of subsequent anti-cancer therapy. Whenever possible, optional on-treatment and disease progression tumor biopsies should be collected from the same or similar location as the pre-treatment tumor tissue sample. Participation in the Optional Research portion of the study is not available at sites in China.

[x] BLOOD SAMPLE FOR ctDNA - Fresh blood sample collected at screening is required from all patients for submission to FMI, or to the alternative Sponsor-designated central testing laboratory in regions where FMI is not available.

[y] PLASMA SAMPLE FOR SOMATIC MUTATION DETERMINATION - Plasma samples for somatic mutation determination are to be collected prior to dosing on Days 1 and 15 of Cycle 1, Day 1 of Cycle 2, then Day 1 of every third cycle thereafter beginning with Cycle 3 (i.e., Cycles 3, 6, 9, etc.), and at the treatment discontinuation visit. In the event of repeated attempts at a Cycle "x" Day 1, this sample is only collected at the first Day 1 attempt and not repeated. For sites in China, only plasma samples collected at Cycle 1 Day 15 and the treatment discontinuation visit are required.

[z] BLOOD SAMPLE FOR BIOMARKER NGS - Blood sample for NGS is to be collected prior to dosing on Day 1 of Cycle 1. These samples are not to be collected at sites in China.

[aa] BLOOD SAMPLE FOR WGS - Blood sample for WGS is to be collected prior to dosing on Day 1 of Cycle 1 unless prohibited by local regulations. These samples are not to be collected at sites in China.

[bb] Inavolisib/PLACEBO ADMINISTRATION - Inavolisib/placebo will be administered as 9-mg tablet dose PO QD on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1. In the event of a palbociclib dosing cycle delay on the planned Day 1 of any Cycle, inavolisib may continue QD dosing if medically appropriate. For patients participating in MN, the mobile nurse will coordinate the administration of inavolisib/placebo, and can advise on the completion of the patient dosing diary.

[cc] PALBOCICLIB ADMINISTRATION - Palbociclib will be administered as 125-mg capsule or tablet dose taken PO QD on Days 1–21 of each 28-day cycle, beginning on Day 1 of Cycle 1. In the event palbociclib administration is held due to an adverse event on Day 1 of a given cycle, the palbociclib dosing cycle should not begin until the patient is able to resume administration, which will correspond to a delayed Day 1 visit. All subsequent visits in that cycle will be based on the delayed Day 1 visit. As such, the cycle will be extended past 28 days. If appropriate, Inavolisib/Placebo administration may be continued daily, and fulvestrant administration may be continued approximately every 4 weeks, independently from the start of the palbociclib dosing cycle. For patients participating in MN, the mobile nurse will coordinate the administration of palbociclib if the MN visit corresponds with a palbociclib dosing day and can advise on the completion of the patient dosing diary.

[dd] FULVESTRANT ADMINISTRATION - Fulvestrant will be administered as 500-mg IM injection (two IM injections of 250 mg each) on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks independent of palbociclib cycles. In the event of a palbociclib dosing cycle delay on the planned Day 1 of any Cycle, fulvestrant may continue dosing approximately every 4 weeks if medically appropriate. For patients participating in MN, fulvestrant may be administered by a mobile nurse.

[ee] CONCOMITANT MEDICATIONS - Medications (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 30 days after the final dose of study treatment. In addition, an Analgesics eCRF will be utilized to collect specific information regarding pain management at specific timepoints.

[ff] LHRH AGONIST TREATMENT & MONITORING – When applicable, treatment with an LHRH agonist must begin ≥ 14 days prior to C1D1. LHRH agonist should be administered in a monthly formulation. Patients receiving an LHRH agonist should be monitored at least every 3 months to confirm complete ovarian function suppression. For patients receiving LHRH agonist and participating in MN, LHRH agonist may be administered by a mobile nurse.

[gg] **ADVERSE EVENTS** - After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment, or until initiation of another anti-cancer therapy, whichever occurs first. After the end of treatment and the 30-day safety follow-up visit, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to study drug treatment. Mobile nurses will be properly trained by MN vendor on how to identify and record all adverse events in accordance with the instructions and within protocol-mandated reporting period. The investigator must review and assess the adverse events prior to recording of the events in eCRF (Section 5.3).

[hh] **PATIENT-REPORTED OUTCOMES** - Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of all other assessments, and prior to the administration of study treatment, except that clinical laboratory samples may be collected prior to administration of PRO questionnaires. Questionnaires EORTC QLQ-C30 (Appendix 4), BPI-SF worst pain item and EQ-5D-5L (Appendix 8) will be administered at baseline (i.e., Day 1 of Cycle 1), on planned Day 1 of Cycles 2 and 3, at planned Day 1 of every other cycle starting at Cycle 5 (i.e., Cycle 5, Cycle 7, etc.), at the treatment discontinuation visit; during the post-treatment follow-up they will be completed every 8 weeks during the first 2 years, then every 12 weeks thereafter until PD. The BR23 will be administered at baseline, planned Day 1 of Cycles 5, 11, 17 and every 6 cycles (e.g., Cycle 23, Cycle 29) through planned Cycle 47 Day 1, at the treatment discontinuation visit; during the post-treatment follow-up they will be completed every 8 weeks during the first 2 years, then every 12 weeks thereafter until PD. On those cycles, the BR23 is to be given immediately after the QLQ-C30. The NCI PRO-CTCAE (Appendix 7) will be administered at baseline (i.e., Day 1 of Cycle 1), on planned Days 1 and 15 of Cycles 1–3, on planned Day 1 of every other cycle thereafter (Cycle 5, Cycle 7, etc.), at treatment discontinuation visit, and during the "Post-treatment Tumor Assessment follow-up with PRO Collection", when applicable (refer to footnote "u"). The Day 1 PROs for any cycle are not to be completed again in the event that it is determined following completion of the PROs that the day 1 of the given palbociclib cycle will be delayed. Additionally, the timing of any subsequent PRO assessments will be based on the actual Day 1 of the given cycle (e.g., if it is determined that the start of palbociclib at Cycle 3 will be delayed a week, the Day 15 PRO-CTCAE will occur two weeks after the start of palbociclib, and the Cycle 4 Day 1 assessment will occur when the next Day 1 administration of palbociclib is planned. For patients participating in MN, if the Day 15 of Cycle 2 or 3 visit is conducted via MN, the mobile nurse should confirm that the PRO-CTCAE questionnaire has been completed via website prior to beginning the MN assessments. For patients who permanently discontinue study treatment for reasons other than progressive disease, PROs will be completed according to the schedule of tumor assessments. Following disease progression, patients should have an additional PRO assessment during survival follow-up (i.e., at the first 90-day/3-month mark). This PRO assessment may be conducted in clinic or via web portal if the patient is unable to attend.

[ii] **MID-CYCLE TELEPHONE CALL** - Mid-cycle telephone call starting on Day 15 of Cycle 4 and continuing on Day 15 of every cycle thereafter. Telephone call from the site to the patient to assess adverse events as well as concomitant medications. This telephone call will allow site staff to implement adequate adverse event management in a timely manner once clinic visits decrease to every 28 days.

[jj] **POST-TREATMENT ANTI-CANCER THERAPY** - After study treatment discontinuation, all patients will be followed for subsequent anti-cancer therapies. These data will be collected via telephone calls and/or clinic visits during the post-treatment follow-up and survival follow-up, approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

[kk] **SURVIVAL** - After study treatment discontinuation and post-treatment follow-up, all patients will be followed for survival. These data will be collected via telephone calls and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Appendix 2
Schedule of Pharmacokinetic Sampling

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Predose [a]	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
	3 hours (±30 min) post-dose	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
Cycle 1, Day 8 [b]	Predose [a]	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
Cycle 1, Day 15	Predose [a]	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
	3 hours (±30 min) post-dose	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
Cycle 2, Day 15 [b]	Predose [a]	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)

PK=pharmacokinetic.

Notes: Dose time on the day before and day of PK sampling should be accurately reported.

PK sampling timepoint should be accurately reported.

[a] The blood samples will optimally be obtained within 5 minutes prior to dosing but may be obtained up to 2 hours prior to dosing.

[b] For patients at participating sites who have provided written informed consent to participate in optional mobile nursing, blood samples (shaded in gray in the table above) can be collected by a mobile nurse.

Appendix 3
Schedule of Intense Pharmacokinetic Sampling in Chinese Patients

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Predose [a]	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
	0.5 hour post-dose (±5 min)	Inavolisib PK (plasma)
	1 hour post-dose (±5 min)	Inavolisib PK (plasma)
	2 hours post-dose (±15 min)	Inavolisib PK (plasma)
	3 hours (±30 min) post-dose	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
	8 hours post-dose (±30 min)	Inavolisib PK (plasma)
Cycle 1, Day 2	24 hours post-dose (±2 hr)	Inavolisib PK (plasma)
Cycle 1, Day 8	Predose [a]	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
Cycle 1, Day 15	Predose [a]	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
	0.5 hour post-dose (±5 min)	Inavolisib PK (plasma)
	1 hour post-dose (±5 min)	Inavolisib PK (plasma)
	2 hours post-dose (±15 min)	Inavolisib PK (plasma)
	3 hours (±30 min) post-dose	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)
	8 hours post-dose (±30 min)	Inavolisib PK (plasma)
Cycle 1, Day 16	24 hours post-dose (±2 hr)	Inavolisib PK (plasma)
Cycle 2, Day 15	Predose [a]	Inavolisib PK (plasma)
		Palbociclib PK (plasma)
		Fulvestrant PK (plasma)

PK = pharmacokinetic.

Notes: Dose time on the day before and day of PK sampling should be accurately reported. PK sampling timepoint should be accurately reported.

[a] The blood samples will optimally be obtained within 5 minutes prior to dosing but may be obtained up to 2 hours prior to dosing.

Appendix 4
European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ-C30)

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

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

Appendix 5
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Breast Cancer Module (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

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

Appendix 6
Brief Pain Inventory-Short Form "Worst Pain" Item

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Please rate your pain by circling the one number that best describes your pain at its worst in the last week.										
0 No Pain	1	2	3	4	5	6	7	8	9	10 Pain as bad as you can imagine

Appendix 7
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
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

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

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

Appendix 8
European Quality of Life 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire

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Health Questionnaire

English version for the USA

Appendix 8: European Quality of Life 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire

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

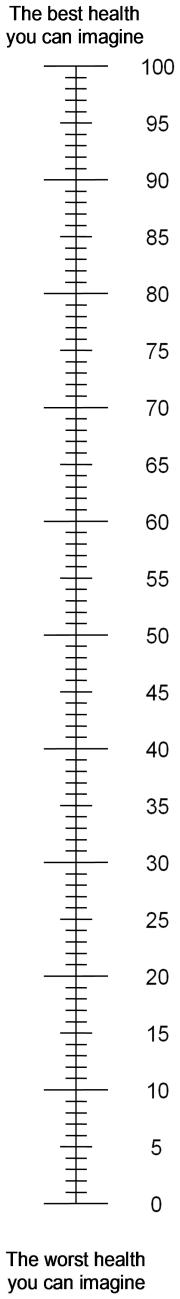
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 9
Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 10
FoundationOne® Liquid CDx Assay Coverage of *PIK3CA*

Covered *PIK3CA* Exon	Eligible Amino Acid / Codon of Interest Captured
2	R88, G106, K111, G118
3	n/a
5	N345
6	n/a
7	n/a
8	C420, E453
10	E542, E545, Q546
14	n/a
19	n/a
21	M1043, H1047, G1049

n/a = not applicable as no trial eligible mutation exists in this codon, despite coverage for the exon; *PIK3CA* = gene encoding phosphatidylinositol 3-kinase alpha.

Appendix 11
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication

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

Measurability of Tumor at Baseline

Definitions

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

Measurable Tumor Lesions

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

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

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

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

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

Non-measurable Tumor Lesions

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

Special Considerations Regarding Lesion Measurability

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

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

Target Lesions: Specifications by Methods of Measurements

a. Measurement of Lesions

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

b. Method of Assessment

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

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

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

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should

be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

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

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

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

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

Baseline Documentation of Target and Non-Target Lesions

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

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

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short

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

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

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

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

Response Criteria

a. Evaluation of Target Lesions

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

- Complete response (CR): Disappearance of all target lesions
- Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$ 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum *in the* study (nadir), including baseline
- In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

- The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum *in the* study

b. Special Notes on the Assessment of Target Lesions

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

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

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

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

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

c. Evaluation of Non-Target Lesions

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

- Complete response (CR): Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
- All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- Progressive disease (PD): Unequivocal progression of existing non-target lesions
- The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

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

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

nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

Bone-Only Disease:[3] Since bone lesions are not considered measurable, patients with bone-only disease will be evaluated for progression only. Progression is defined as the appearance of new lytic lesions or other new bone destruction thought to be related to cancer by X-ray, CT scan or MRI, or a bone event requiring intervention (surgery) if not associated with trauma or other obvious cause. Changes in bone scan or ^{18}F NaF PET scan should not be used to define progression. Any changes in bone imaging should be evaluated radiographically by X-ray, CT scan, or MRI to ascertain the presence of bone destruction versus a healing reaction. The appearance of new lesions on bone scan or ^{18}F NaF PET scan may constitute progressive disease if associated with clinical symptoms suggestive of disease progression. The occurrence of a pathologic fracture at a site previously recognized for bone disease may constitute progressive disease if not associated with trauma or other obvious cause. Bone pain requiring radiation will constitute progressive disease. Increase in pain at a site of previously recognized bone disease may constitute progressive disease if it is persistent and not associated with other obvious cause.

e. New Lesions

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

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

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

[3] Reminder that patients with non-measurable *(*evaluable*)* bone-only disease are not to be enrolled in this study.

there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Response

a. Timepoint Response (Overall Response)

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

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

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

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

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

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

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

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

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

b. Missing Assessments and Not-Evaluable Designation

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

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

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a

descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1–Table 3.

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

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

Appendix 12
American Joint Committee on Cancer TNM Classification of Malignant Tumors

Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension

Tumor (T)

T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension
T3	Tumor > 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules)[a]
T4a	Extension to the chest wall [b]
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma

Reprinted with permission from AJCC: Breast. In: Edge SB, Greene FL, Byrd DR, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp 619–620.

DCIS = ductal carcinoma in situ.

Note: The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cut-off for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cut-off. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

[a] Invasion of the dermis alone does not qualify as T4.

[b] Invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4.

Regional Lymph Nodes (N)

Clinical	
cNX [a]	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
cN1mi [b]	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted
	OR
	Metastases in ipsilateral mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes and in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement
	OR
	Metastases in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases
	OR
	Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)

Regional Lymph Nodes (N)

Clinical	
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

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

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

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

Pathological (pN)

pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathologic study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters ≤0.2 mm)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases
	OR
	Metastases in 1–3 axillary lymph nodes
	AND/OR
	Clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells >0.2 mm but none >2 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis >2 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined

Pathologic (pN)

pN2	Metastases in 4–9 axillary lymph nodes
	OR
	positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit $>$ 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in $\geq$ 10 axillary lymph nodes
	OR
	Metastases in infraclavicular (Level III axillary) lymph nodes
	OR
	Metastases in ipsilateral internal mammary lymph nodes detected by imaging in the presence of one or more positive Level I, II axillary lymph nodes
	OR
	Metastases in $>$ 3 axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes
	OR
	Metastases in ipsilateral supraclavicular lymph nodes

Pathologic (pN)

pN3a	Metastases in ≥ 10 axillary lymph nodes (at least 1 tumor deposit > 2.0 mm)
	OR
	Metastases to the infraclavicular (Level III axillary lymph) nodes.
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging)
	OR
	pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Note: (sn) and (f) suffixes should be added to the **N** category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy, respectively, with NO further resection of nodes.	

Distant Metastases (M)

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

Anatomic Stage/Prognostic Groups [a]

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

Stage	T	N	M[c]
IV	Any T	Any N	M1

[a] T1 includes T1mi.

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

[c] M0 includes M0(i+); The designation pM0 is not valid; any M0 should be clinical. If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence or disease progression, and provided the patient has not received neoadjuvant therapy.

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