Official Title: **A Phase II Randomized, Double-Blind, Study of Ipatasertib (GDC-0068), an Inhibitor to AKT, in Combination With Paclitaxel as Neoadjuvant Treatment for Patients With Early Stage Triple Negative Breast Cancer**

NCT Number: NCT02301988

Document Date: Protocol Version 3: 19 Jan 2016

PROTOCOL

TITLE:	**A PHASE II RANDOMIZED, DOUBLE-BLIND, STUDY OF IPATASERTIB (GDC-0068), AN INHIBITOR TO AKT, IN COMBINATION WITH PACLITAXEL AS NEOADJUVANT TREATMENT FOR PATIENTS WITH EARLY STAGE TRIPLE–NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	GO29505
VERSION NUMBER:	3
EUDRACT NUMBER:	2014-003029-16
IND NUMBER:	111051
TEST PRODUCT:	Ipatasertib (GDC-0068; RO5532961)
MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 14 August 2014
DATES AMENDED:	Version 2: 23 July 2015 Version 3: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	19-Jan-2016 19:25:56

PROTOCOL AMENDMENT, VERSION 3
RATIONALE

Protocol GO29505 has been amended to include the following changes:

- Wording regarding dosing delay due to treatment-related toxicity (Section 5.1.5.1) has been added to clarify that when dosing delay to paclitaxel occurs, preferred dosing for ipatasertib/placebo is to align and resume with paclitaxel dosing
- To clarify that dose reductions and dose modification(s) for ipatasertib/placebo and paclitaxel are independent (Table 1)
- To provide further guidance and clarification to the management of diarrhea

  Dosing modification for ipatasertib and placebo (Section 5.1.5.2)

  Diarrhea management (Section 5.1.5.6)
- To add Grade $\geq$3 diarrhea and Grade 2 diarrhea that persists for longer than 5 days despite optimal medical management (per diarrhea management in Section 5.1.5.6) as adverse event of special interest in Section 5.2.3 to improve monitoring of diarrhea events by the Sponsor
- Wording regarding recording of persistent or recurrent adverse events (Section 5.3.5.3) has been modified/added to clarify data entry requirements for adverse event reporting
- To add a sensitivity analysis that accounts for patients whose pCR assessment cannot be ascertained (Section 6.4.1).
- To include additional information on the management guideline for diarrhea (Appendix 6)

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

PROTOCOL AMENDMENT, VERSION 3
SUMMARY OF CHANGES

GLOBAL CHANGE

The Medical Monitor has been changed to [redacted] M.D.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 3.1.2: Joint Monitoring Committee

A Joint Monitoring Committee (JMC) will be in place during the study and will provide oversight of safety and efficacy. The primary responsibility of the JMC is to review the available safety data and to make a recommendation to continue, modify the study design as required for improved safety, or terminate the study. *While a JMC review is being conducted, patient accrual into the study will continue.* The JMC will be composed of a designated sponsor medical oncologist (who is not the study medical monitor), the drug safety officer, and the study biostatistician. In addition, *the* JMC will also include at least two external medical oncologists who are not employees of Roche/Genentech and are not affiliated with the study team, to provide clinical and methodological expertise in early breast cancer. The members of the JMC will not interact with the sites or investigators in terms of study conduct.

~~The JMC will convene to review partially unblinded summaries of the safety data after approximately 20 patients have completed study treatment, including surgical resection. In addition, after approximately 90 patients have completed study treatment as well as surgery, the JMC will convene again to review data from an interim safety and efficacy analysis. Additional details (e.g., JMC members, communication, affiliations) will be provided in the JMC Agreement. While this review is being conducted, patient accrual into the study will continue. The medical monitor may also request additional safety and/or efficacy analysis and may call for additional meetings of the JMC to review ongoing data to assess risk/benefit.~~

The reviews the JMC will conduct are described in Section 6.8.1 and Section 6.8.2.

SECTION 4.3.2.2: Paclitaxel

The dose of paclitaxel in this study is 80 mg/m^2 administered by IV infusion on Days 1, 8, 15, and 22 of each 4-week cycle, for a total of 3 cycles of treatment *(12 total doses)*….

SECTION 5.1.2: Safety Monitoring

Safety will be evaluated in this current study through the monitoring of all serious adverse events, non-serious adverse events, and laboratory abnormalities, defined and graded according to NCI CTCAE, v4.0. ~~In addition, prespecified analyses of the safety and relevant efficacy data will be conducted by the JMC after approximately 20 patients have completed study treatment including surgery (safety only), and again after~~

~~approximately 90 patients have completed study treatment including surgery (safety and efficacy~~*In addition, the JMC will conduct analyses of safety (see Section 6.8.1 and Section 6.8.2*).

SECTION 5.1.5.1: General Guidelines

General guidelines for dosage/schedule modification are summarized as follows:

- ~~If paclitaxel treatment component is delayed, the study cycle day count for each cycle continues and does not shift.~~
- If ipatasertib or placebo treatment is delayed, paclitaxel treatment should continue *as scheduled; however, if paclitaxel treatment is delayed and ipatasertib/placebo is scheduled to be administered at the same timepoint, it is preferred that ipatasertib/placebo is also delayed to align with paclitaxel dosing*.
- ~~If the dose day of paclitaxel treatment is delayed, the ipatasertib or placebo may be delayed at the discretion of the investigator.~~

SECTION 5.1.5.2: Dosage Modification for Ipatasertib and Placebo

If the patient does not tolerate the QD dosing of the ipatasertib or placebo, a BID regimen of the ipatasertib or placebo (with the total daily dose divided in half, without a dose reduction, and administered approximately every 12 hours) may be attempted (e.g., a 400 mg QD dose may be divided into 200 mg administered BID). The BID regimen may be used to alleviate gastrointestinal symptoms, including nausea~~,~~ *and* vomiting~~, and/or diarrhea~~. Employment of a BID regimen should not be considered as a dose reduction. No more than two dose reductions of ipatasertib or placebo per patient (lowest dose level to be administered will be 200 mg/day) will be allowed, and dose re-escalation of ipatasertib or placebo may be permitted in the study after discussion with the Medical Monitor.

SECTION 5.1.5.6: Diarrhea

Diarrhea should be managed with loperamide or per ~~institutional guidelines.~~*local guidelines and standard of care, including but not limited to therapy with Lomotil (diphenoxylate and atropine), codeine, or octreotide.* Dose reductions for diarrhea should occur only if the symptoms persist despite treatment with adequate (combination) anti-diarrheal medications. If persistent diarrhea *(more than 48 hours despite optimal medical treatment or dose hold)* is attributable to the ipatasertib or placebo, and/or paclitaxel, dosage modification guidelines for ipatasertib or placebo, and/or paclitaxel are outlined below:

- Grade 2 diarrhea: The investigator *should initiate optimal medical management with loperamide as early as possible. If diarrhea is persistent (lasting longer than 48 hours despite medical management), second-line therapy* may ~~employ a BID regimen~~*include (but not limited to) Lomotil (diphenoxylate and atropine), codeine or octreotide per local guidelines and standard* of *care. Ipatasertib/placebo dosing should be interrupted until improvement of diarrhea to Grade ≤ 1, at which time* ipatasertib ~~administration (equivalent to~~*/placebo may be resumed at* the ~~total daily~~*same* dose ~~divided by half), see Section 0. Alternatively, the investigator may~~

~~also~~*for initial occurrence with consideration of maintenance loperamide dosing (i.e., 2 mg, 2 to 4 times daily). Investigators may* reduce ipatasertib or placebo by one dose level (see Table 1) *for recurrent Grade 2 diarrhea*. If diarrhea persists following *up to two* dose reduction*s* of ipatasertib or placebo, consider dose hold ~~or reduction~~ of paclitaxel ~~by one~~. *Dose intensity of paclitaxel should be maintained as much as is safely possible. Paclitaxel* dose ~~level~~ *reduction or discontinuation can be considered if diarrhea persists even after ipatasertib/placebo discontinuation* (see Table 1).

- Grade ≥3 diarrhea: Medical management of diarrhea per Grade 2 diarrhea above should be initiated as early as possible. Ipatasertib or placebo should be held until the diarrhea resolves to Grade ≤~~2~~1, at which time maintenance loperamide dosing (i.e., 2 mg, 2 to 4 times daily) is recommended. The dose of ipatasertib or placebo will be reduced by one dose level when treatment resumes (see Table 1). If diarrhea persists following dose reduction of ipatasertib or placebo, ~~consider~~an additional dose hold or reduction ~~of paclitaxel by one dose level~~with ipatasertib/placebo should be considered (see Table 1). Dose intensity of paclitaxel should be maintained as much as is safely possible. Paclitaxel dose reduction or discontinuation can be considered if diarrhea persists even after ipatasertib/placebo discontinuation *(see Table 1)*.

Dose re-escalation of the ipatasertib or placebo, and/or paclitaxel may be permitted in subsequent cycles for patients who exhibit Grade ≤~~2~~*1* diarrhea for at least one cycle *after discussion with the Medical Monitor*.

For additional information on the management guideline for diarrhea, see Appendix 6.

SECTION 5.2.3: Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

…Adverse events of special interest for this study include the following:

- Grade ≥3 colitis *or diarrhea*
- *Grade 2 diarrhea that persists for longer than 5 days despite optimal medical management (per diarrhea management in Section 5.1.5.6)*

SECTION 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~~ *, unless the* severity ~~(intensity or grade) of the event will be recorded at the time the event is first reported.~~*increases.* If a persistent adverse event becomes more severe, ~~the most extreme severity~~*it* should ~~also~~ be recorded *as a separate event* on the Adverse Event eCRF. *The initial (less severe) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became more severe.* If ~~the~~*a persistent adverse* event becomes serious, it should be *recorded as a separate event on the Adverse Event eCRF and* 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 "~~*initial (*non-~~-~~serious~~" to "~~*) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became* serious~~," providing the date that the event became serious, and completing all data fields related to serious adverse events~~.

SECTION 6.4.1: Primary Efficacy Endpoint

In addition, a sensitivity analysis may be conducted to account for patients whose pCR assessment cannot be ascertained.

Section 6.8.2: Optional Interim Analysis

In addition, the Medical Monitor may request additional safety analysis and may call for additional meetings of the JMC to review ongoing data to assess risk/benefit.

Table 1: Suggested Dose Reductions for Ipatasertib, Placebo, and/or Paclitaxel

Table 1 has been updated to reflect changes to the protocol.

Figure 2: Study Schema

Figure 2 has been updated to reflect changes to the protocol.

APPENDIX 6: *Management Guideline for Diarrhea*

Appendix 6 has been added to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II RANDOMIZED, DOUBLE-BLIND, STUDY OF IPATASERTIB (GDC-0068), AN INHIBITOR TO AKT, IN COMBINATION WITH PACLITAXEL AS NEOADJUVANT TREATMENT FOR PATIENTS WITH EARLY STAGE TRIPLE–NEGATIVE BREAST CANCER**
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MEDICAL MONITOR:	[redacted] *M.D.*
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II RANDOMIZED, DOUBLE-BLIND, STUDY OF IPATASERTIB (GDC-0068), AN INHIBITOR TO AKT, IN COMBINATION WITH PACLITAXEL AS NEOADJUVANT TREATMENT FOR PATIENTS WITH EARLY STAGE TRIPLE–NEGATIVE BREAST CANCER**
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EUDRACT NUMBER:	2014-003029-16
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PHASE:	II
INDICATION:	Breast cancer
SPONSOR:	Genentech, Inc.

Objectives

Efficacy Objectives

The primary efficacy objective for this study is to estimate the efficacy of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in patients with early stage triple-negative breast cancer (TNBC), as measured by local pathology laboratory evaluation of pathological complete response (pCR) rate within the breast and axilla (ypT0/Tis ypN0) in all patients and in patients with phosphatase and tensin homolog (PTEN)-low tumors.

The secondary efficacy objectives for this study are as follows:

- To estimate the clinical activity of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel, as measured by local pathology laboratory evaluations of pCR within the breast (ypT0/Tis) in all patients and in patients with PTEN-low tumors
- To evaluate objective response rate (ORR) assessed by breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in all patients and in patients with PTEN-low tumors
- To estimate the clinical activity, as measured by pCR (ypT0/Tis and ypT0/Tis ypN0) and ORR of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in patients who are Akt diagnostic positive (Dx+) (defined by PTEN status, INPP4B status, and PI3K alterations)
- To assess pCR rates according to subtypes of breast cancer defined by molecular profiles (e.g., the intrinsic subtypes of breast cancer defined by the PAM50 classifier)
- To assess the rates of breast-conserving surgery (BCS) and conversion to BCS of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in women with T2 or T3 tumors

Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of ipatasertib combined with paclitaxel versus placebo combined with paclitaxel.

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of GDC-0068 using a sparse sampling methodology, when given in combination with paclitaxel in early stage TNBC patients.

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To assess the effect of PI3K/Akt pathway alterations on pCR in patients treated with ipatasertib combined with paclitaxel versus placebo combined with paclitaxel, based on exploratory analysis of tumor tissue using molecular data obtained by one or more of the following analyses:

  Mutation and RNA/DNA copy number changes in oncogenes, tumor suppressors, and/or other genes associated with TNBC response to treatment and progression by DNA sequencing and/or in situ hybridization (ISH)

  Levels of Akt pathway proteins, as evaluated by reverse phase protein array

  Levels of tumor suppressors and/or receptor tyrosine kinases by immunohistochemistry (IHC)
- To evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess the exposure-response relationships for efficacy, safety, and biomarker data

Study Design

Description of Study

This is a randomized, double-blind, placebo-controlled, multicenter, pre-operative Phase II study designed to estimate the efficacy of ipatasertib combined with paclitaxel chemotherapy versus placebo combined with paclitaxel chemotherapy in women with Stage Ia–IIIa (primary tumors $\geq$1.5 cm) triple-negative breast adenocarcinoma. Patients with cT4 or cN3 tumors are not eligible. Patients and investigators will be blinded to study treatment. Estrogen receptor (ER)- and Progesterone receptor (PgR)-negative is defined as $<$1% of tumor cell expression of ER and PgR. Patients who have an unknown ER, PgR, or human epidermal growth factor 2 (HER2) status and for whom determination of status is not possible are also not eligible for this study. Estimated benefit will be compared in all patients (independent of results from the diagnostic assessments of the tumor) and in patients with PTEN-low tumors.

Approximately 150 patients will be enrolled at approximately 30 centers. Patients will be randomized in a 1:1 ratio, stratified by the following three factors: PTEN status (H score 0, vs. 1 to $\leq$150, vs. $>$ 150), node involvement (pathologically positive versus no known involvement), and T size (T1–2 vs. T3).

For the purpose of enrollment, ER, PgR, and HER2 will be locally determined prior to beginning of study treatment. Additionally, all enrolled patients must consent to provide sufficient and evaluable archival tissue for PTEN status determination. In the absence of archival tissue, fresh tissue biopsy samples, excluding cytology and fine-needle aspiration (FNA) specimens, will be acceptable; however, evaluation of the patient's tumor sample for PTEN status by a central laboratory should occur prior to the initiation of study treatment. All patients will undergo pretreatment tumor tissue acquisition (snap-frozen, optimal cutting temperature [OCT], and formalin-fixed paraffin-embedded [FFPE] cores). One pretreatment FFPE core biopsy and two freshly frozen core biopsies must be obtained for all patients prior to initiating study treatment. Pre-surgical FNA or core biopsy of suspicious node is allowed, but full excision lymph node biopsy (e.g., sentinel lymph node excisional biopsy [SLNB]) is not allowed.

All patients will receive paclitaxel 80 mg/m^2 every 7 days for a total of 12 doses *(i.e., Days 1, 8, 15, and 22 of each cycle)*. Patients in the experimental arm will receive ipatasertib at a dose of 400 mg administered orally once daily (QD) on Days 1 to 21 every 28 days and those in the control arm will receive placebo on the same days. Each cycle will be 28 days in duration and study treatment will continue for a total of three cycles until disease progression, intolerable

toxicity, elective withdrawal from the study, or study completion or termination. Following three cycles of treatment, patients will undergo surgery.

Prior to administration of the second paclitaxel dose, a second research biopsy will be conducted for biomarker evaluation; at least one FFPE and at least two frozen OCT cores biopsy samples will be obtained.

Primary breast tumor and axillary lymph nodes will be assessed every 4 weeks until Week 13 by clinical breast exam (palpation and clinical measurement; caliper preferred). Suspicion of progression based on clinical exam should be further evaluated. Tumor measurement by MRI for disease evaluation will be performed at screening and prior to surgery (at approximately Weeks 10–12, following completion of neoadjuvant chemotherapy). Early assessment by MRI is allowed for suspected progression. Estimation of ORR will be by modified RECIST.

Patients with clinical or radiologic evidence of significant residual or progressive disease, as defined by modified RECIST, can either proceed directly to surgery or be discontinued from the study, based on the investigator's discretion. Patients who discontinue study treatment prior to surgery will be required to have an additional research biopsy where at least one FFPE and at least two frozen OCT core biopsy samples will be obtained.

Safety will be evaluated during the study through the monitoring of all serious and nonserious adverse events, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE, v4.0).

The pharmacokinetics of ipatasertib/placebo will be assessed in all patients.

During Weeks 10–12 (approximately; i.e., near the time of completion of neoadjuvant chemotherapy), the patient will consult with the surgeon to plan the type of breast surgery to be performed (breast conservative vs. mastectomy) and to schedule the date for surgery.

Following surgical resection of primary tumor, patients are expected to continue post-operative treatment with a standard adjuvant chemotherapy regimen such as 5-FU/doxorubicin/cyclophosphamide (FAC), 5-FU/epirubicin/cyclophosphamide (FEC), or doxorubicin/cyclophosphamide (AC), if appropriate and as chosen by their treating physician. Post-operative treatment information (chemotherapy, radiotherapy, etc.) will be collected at the post-surgery visit.

The primary efficacy endpoint, pCR within the breast and axilla (ypT0/Tis ypN0) in all patients and in patients with PTEN-low tumors will be assessed by local pathology evaluation following completion of neoadjuvant therapy and surgery.

The trial is anticipated to have a recruitment period of approximately 24 months.

Number of Patients

Approximately 150 patients will be enrolled at approximately 30 centers.

Target Population

Patients with early stage (Stage Ia–IIIa; primary tumors ≥1.5 cm) triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for this breast cancer may be eligible for this study.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Premenopausal or postmenopausal women, age ≥18 years
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Histologically documented triple-negative carcinoma of the breast with all of the following characteristics:

  Primary tumor ≥1.5 cm in largest diameter (cT1–3) by MRI. In the case of a multifocal tumor (defined as the presence of two or more foci of cancer within the same breast quadrant), the largest lesion must be ≥1.5 cm and designated as the "index" lesion for all subsequent tumor evaluations.

  Stage I to operable Stage IIIa breast cancer

- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for PTEN status by central histopathology laboratory

  Specimen may consist of a tissue block (preferred) or 10 unstained, serial slides. Cytologic or FNA samples are not acceptable.

  If archival tissue is either insufficient or unavailable, FFPE core sample from a pretreatment biopsy of the tumor may be used.

  Cytologic or FNA samples are not acceptable.
- Adequate hematologic and organ function within 14 days before the first study treatment, defined by the following:

  Neutrophils (absolute neutrophil count [ANC] $\geq 1500/\mu L$)

  Hemoglobin ≥ 9 g/dL

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

  Serum albumin ≥ 2.5 g/dL

  Total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN) with the following exception:

  Patients with known Gilbert's disease who have serum bilirubin $\leq 3 \times$ ULN may be enrolled

  AST and ALT $\leq 2.0 \times$ ULN

  Alkaline phosphatase $\leq 2 \times$ ULN

  PTT and/or either international normalized ratio (INR) or prothrombin time (PT) $\leq 1.5 \times$ ULN (except for patients receiving anticoagulation therapy).

  Patients receiving heparin treatment should have an activated partial prothrombin time (aPTT) between 1.5 to $2.5 \times$ ULN (or patient value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 to 4 days apart.

  Fasting serum glucose ≤ 150 mg/dL (8.33 mmol/L) and HbA1C $\leq 8\%$
- Able to comply with the study protocol, in the investigator's judgment
- For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 6 months after the last dose of study drug

  Abstinence is acceptable only if it is in line with 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.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include tubal ligation, male sterilization, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $< 1\%$ per year. Barrier methods must always be supplemented with the use of a spermicide.

<u>Exclusion Criteria</u>

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

- Known HER2-positive, ER-positive, or PgR-positive breast cancer

  HER2 positivity is defined as one of the following: On IHC testing, $> 10\%$ of contiguous and homogeneous tumor cells show protein overexpression (IHC 3+) or on ISH testing, or gene amplification (HER2 copy number or HER2/CEP17 ratio by ISH based on counting at least 20 cells within the area). If results are equivocal, reflex testing should be performed using an alternative assay (IHC or ISH).

  ER and PgR positive are defined as $\geq 1\%$ of cells expressing hormonal receptors via IHC analysis.

Patients who have not had HER2, ER, or PgR testing, and thus, the HER2, ER, and PgR status of the breast adenocarcinoma is unknown, are not eligible.

- Any prior treatment for the current primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer (Note: Staging exams are at the discretion of the investigator).
- Bilateral invasive breast cancer
- Multicentric breast cancer (the presence of more than one tumor in different quadrants of the breast)
- Patients who have undergone excisional biopsy of primary tumor and/or axillary lymph nodes
- Patients who have undergone excisional SLNB prior to study treatment

  Pre-surgical FNA or core biopsy of suspicious node is allowed.
- Any contraindication to MRI examination, including the following:

  Neurostimulators

  Pacemakers

  Implanted metallic material or devices (metal implants or large tattoos in the field of view)

  Severe claustrophobia

  Physical characteristics (weight and/or size) that exceed the capabilities of the MRI scanner

  Known allergy or hypersensitivity reactions to gadolinium, versetamide, or any of the inert ingredients in gadolinium-based contrast agents

  Severe renal insufficiency, e.g., estimated glomerular filtration rate <30 mL/min
- Need for chronic corticosteroid therapy of ≥ 20 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Known hypersensitivity or contraindication to any component of the study treatments, including paclitaxel excipient macrogolglycerol ricinoleate
- Grade ≥ 2 peripheral neuropathy
- History of Type I or Type II diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment
- New York Heart Association (NYHA) Class II, III, or IV heart failure or left ventricular ejection fraction $<50\%$, or active ventricular arrhythmia requiring medication
- Current unstable angina or history of myocardial infarction within 6 months prior to Cycle 1, Day 1
- Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- Congenital long QT syndrome or screening corrected QT interval (QTc) $>$ 480 milliseconds
- History of malabsorption syndrome, lack of physical integrity of the upper gastrointestinal tract, or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Active infection requiring intravenous (IV) antibiotics
- Known HIV infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., Hepatitis B or Hepatitis C virus), current alcohol abuse, or cirrhosis

- Pregnant or lactating, or intending to become pregnant during the study

  Women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Malignancies other than TNBC within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, ductal carcinoma in situ treated surgically with curative intent); medical monitor will make final determination for cancers not mentioned here.
- Active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis)
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

Length of Study

The length of the study is approximately 3 years, including an enrollment period of approximately 24 months, a 4-week screening period, and a 24-week study period.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) 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. LPLV is expected to occur approximately 7 months after the last patient is enrolled.

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measure in all patients and in patients who have PTEN-low tumors is as follows:

- pCR rate in breast and axilla as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system by local pathology evaluation.

The secondary efficacy outcome measures in all patients and in patients who have PTEN-low tumors or who are Akt Dx+, are as follows:

- Objective tumor response by MRI, as assessed by the investigator per modified RECIST
- pCR rate in breast as defined by ypT0/Tis in the American Joint Committee on Cancer staging system by local pathology evaluation
- Comparison of the rates of BCS and conversion to BCS in patients with T2 or T3 tumors

Safety Outcome Measures

The safety and tolerability of ipatasertib when combined with paclitaxel will be assessed using the following outcome measures:

- Incidence, nature, and severity of adverse events, graded according to the NCI CTCAE, v4.0
- Clinically significant changes in vital signs, physical findings, and clinical laboratory results during and following ipatasertib administration

Pharmacokinetic Outcome Measures

For ipatasertib, the following PK parameters will be analyzed using a PopPK approach as data allow:

- Exposure following first dose (AUC_{0-24}) and steady-state (AUC_{ss})
- Minimum observed plasma concentration (C_{min}; trough concentration)
- Apparent clearance following oral dosing (CL/F)

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Alterations in DNA and RNA, including but not limited to mutational status, RNA expression levels, DNA copy number, protein expression and modifications
- Evaluation of changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluation of changes in tumor cellular composition as assessed by diffusion-weighted MRI

Investigational Medicinal Products

Test Product

Ipatasertib (GDC-0068) and Placebo

Ipatasertib will be supplied by the Sponsor.

Study treatment to either ipatasertib or placebo will be assigned by Interactive Web Response System (IWRS). Ipatasertib or placebo will be administered orally QD, beginning on Cycle 1, Day 1 through Day 21 of each 28-day cycle for a total of 3 cycles of treatment. Patients in the experimental arm will receive ipatasertib at a dose of 400 mg QD, and those in the control arm will receive placebo on the same days. Ipatasertib or placebo will be administered prior to the IV infusion of paclitaxel. Each dose of ipatasertib or placebo should be taken with a minimum of 3 ounces (90 mL) of fluid. Ipatasertib or placebo may be taken with or without food. If a dose is missed (not taken within 8 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.

The dose of ipatasertib or placebo will be taken at home, as directed on all days when there are no scheduled clinic visits. Ipatasertib or placebo should be taken at approximately the same time each day. On study visit days or visit days that require a blood draw for PK sampling, patients should not take their dose of ipatasertib or placebo at home before reporting to the clinic. Patients will be instructed to take their oral dose of ipatasertib or placebo at the clinic after completion of the pretreatment assessments.

A sufficient amount of ipatasertib or placebo should be provided to the patient to last for up to one treatment cycle (i.e., approximately 28 days). In some cases, extra tablets may be dispensed if there is a possibility that the patient's next visit may be delayed (e.g., due to holiday, inclement weather, or distance of patient's home from study center). Patients will also be given instructions for self-administration on dosing days that do not coincide with clinic visits.

Patients will be asked to record the time and date they take each dose in a medication diary. Patients will be instructed to bring their bottles of ipatasertib or placebo (including all unused tablets) and their medication diaries to each study visit for assessment of compliance and medication disposal.

The investigator (or designated representative) is responsible for keeping accurate records of the clinical supplies received from the Sponsor, including the amount dispensed to each patient and the amount returned by each patient. Study drug accountability (verification of the total number of tablets administered) for each patient should be performed as indicated in the protocol.

Any dose modification, overdose, or incorrect administration of ipatasertib or placebo should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Paclitaxel

The dose of paclitaxel in this study is 80 mg/m^2 administered by IV infusion on Days 1, 8, 15, and 22 of each 4-week cycle, for a total of 3 cycles of treatment *(12 total doses)*. Calculation of body surface area for the purposes of dosing of paclitaxel should be made according to the prescribing information. If the patient's weight changes by $>$ 10% during the study, the body surface area and drug doses should be recalculated, per institutional guidelines.

On the planned day of treatment, chemotherapy may be administered if:

- ANC $\geq$ 1500/μL (or per institutional guideline)

- Platelet count $\geq$ 100,000/μL (or per institutional guideline)
- Grade $\leq$ 2 clinically significant chemotherapy-related gastrointestinal toxicity

Because of the known potential for allergic reactions to paclitaxel and/or the Cremophor® vehicle, precautions must be taken to decrease the risk of anaphylaxis. Patients must be premedicated prior to paclitaxel per institutional practice with dexamethasone, diphenhydramine, and one of the following two H_2-receptor blockers: ranitidine or famotidine. Other H_2-receptor antagonists, such as cimetidine, which are known to inhibit cytochrome P450, are excluded. An H_1-receptor antagonist, such as diphenhydramine 50 mg IV, may be given as well.

The paclitaxel infusion will be delivered over at least 60 minutes for each dose per institutional guidelines and administered after the oral dose of ipatasertib or placebo.

Patients should be monitored during paclitaxel administration per institutional policies. Patients may receive anti-emetic and other prophylactic treatments (e.g., IV infusions of calcium and magnesium to try and decrease any potential peripheral neuropathy) according to institutional and/or local standards and per manufacturer's instructions.

Any dose modification, overdose, or incorrect administration of paclitaxel should be noted on the Paclitaxel Administration eCRF. Adverse events associated with an overdose or incorrect administration of paclitaxel should be recorded on the Adverse Event eCRF.

Comparator

Ipatasertib placebo is the comparator in this study. See Test Product section above for details.

Statistical Methods

Primary and secondary efficacy analyses will be based on randomized patients, with patients allocated to the treatment arm to which they were randomized.

Safety analyses will include treated patients (i.e., patients who received at least one dose of ipatasertib, placebo, or paclitaxel), with patients allocated to the treatment arm associated with the regimen that they actually received.

No adjustments will be made for multiple comparisons when addressing primary and secondary efficacy endpoints. Multiple comparison adjustments will be used for selected exploratory endpoints to account for genome-wide correlative comparisons.

The primary analysis will be performed after LPLV and subsequent data cleaning, expected to occur approximately 7 months after the last patient has been randomized to the study.

Primary Analysis

The primary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

The primary efficacy endpoint is the rate of locally assessed pCR in breast and axilla (ypT0/Tis ypN0). The primary efficacy analyses will be performed on randomized patients, with the patients allocated to the treatment arm according to the randomization. The pCR endpoint will be analyzed for all randomized patients and for patients with PTEN-low tumors. Patients whose pCR assessment is missing are counted as not achieving a pCR.

An estimate of the pCR rate and its 90% CI (Blyth-Still-Casella method) will be calculated for each treatment arm for all randomized patients and for patients with PTEN-low tumors. The difference in pCR rates will also be provided with 90% CIs, using the normal approximation to the binomial distribution. Stratified Cochran-Mantel-Haenszel tests will be used to compare treatment arms.

In addition, a sensitivity analysis may be conducted to account for patients whose pCR assessment cannot be ascertained.

Determination of Sample Size

This study is designed to evaluate the safety and preliminary evidence of activity of ipatasertib and paclitaxel. This trial is hypothesis-generating and is able to detect only a large benefit from combination therapy with ipatasertib and paclitaxel versus placebo and paclitaxel.

A total of 150 patients will be enrolled in the study (75 per arm). Assuming a 60% prevalence of PTEN-low status in TNBC, it is expected that 90 patients with PTEN-low tumors will be enrolled. This trial will not have adequate power to detect minimum clinically meaningful differences

between treatment arms at a statistically significant α (type 1) error level of 5%. Instead, the 90% confidence intervals (CIs) for the difference in pCR rate will be calculated with the expectation that for clinically meaningful outcomes, the lower limit of the two-sided 90% CI will be greater than 0.

For example, a true improvement of greater than 20% in pCR rate (from 20% to 40%) would be considered a clinically meaningful outcome when comparing ipatasertib and paclitaxel versus placebo and paclitaxel. Given at least 90 patients (45 per arm) with PTEN-low tumors and a targeted improvement of 20% in pCR rate, the corresponding lower limit of the two-sided 90% CI is 2.3%. Also, for 150 patients (75 per arm) in ITT population with a targeted improvement of 15% in pCR rate, the corresponding lower limit of the two-sided 90% CI is 1.5%.

Interim Analyses

Planned Interim Analyses

The Joint Monitoring Committee (JMC) will convene for a review of partially unblinded summaries of the safety data after approximately 20 patients have completed study treatment, including surgery. In addition, after approximately 90 patients have completed study treatment as well as surgery, the JMC will reconvene to perform an interim safety and efficacy analysis. This efficacy interim analysis is for administrative purposes and is not intended to lead to an early termination of the trial if efficacy results appear favorable in a particular treatment arm.

The members, roles, responsibilities, and communication processes of the JMC will be outlined in a separate charter.

Optional Interim Analysis

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct an additional interim efficacy analysis. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and reviewed by the JMC and will follow the communication plan described in the JMC charter.

In addition, the Medical Monitor may request additional safety analysis and may call for additional meetings of the JMC to review ongoing data to assess risk/benefit.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial prothrombin time
AST	aspartate aminotransferase
AUC	area under the curve (total exposure)
$AUC_{0–24}$	exposure following first dose and steady-state
BCS	breast-conserving surgery
BID	twice daily
BUN	blood urea nitrogen
C_{max}	maximum observed concentration
C_{min}	minimum observed plasma concentration
CALGB	Cancer and Leukemia Group B
CEP17	chromosome 17 centromere
CL/F	apparent clearance following oral dosing
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DCIS	ductal carcinoma in situ
DDI	drug-drug interaction
DFS	disease-free survival
DLT	dose-limiting toxicity
Dx+	diagnostic positive
EBC	early breast cancer
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EORTC	European Organisation for the Research and Treatment of Cancer
ER	estrogen receptor
EU	European Union
FDA	U.S. Food and Drug Administration
FNA	fine needle aspiration
FFPE	formalin-fixed paraffin-embedded

Abbreviation	Definition
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HbA_{1C}	glycosylated hemoglobin
H&E	hematoxylin and eosin
HER2	human epidermal growth factor 2
HIPAA	U.S. Health Insurance Portability and Accountability Act
HR	hormone receptor
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
INPP4B	inositol polyphosphate 4-phosphatase, type II
INR	international normalized ratio
IRB	Institutional Review Board
ISH	in situ hybridization
IV	intravenous
IWRS	Interactive Web Response System
JMC	Joint Monitoring Committee
LPLV	last patient, last visit
MBC	metastatic breast cancer
mRNA	messenger RNA
MTD	maximum tolerated dose
mTNBC	metastatic triple-negative breast cancer
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NGS	next-generation sequencing
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic
PopPK	population PK methodology

Abbreviation	Definition
pPRAS40	phosphorylated PRAS40
PgR	progesterone receptor
PRO	patient-reported outcome
PRP	platelet-rich plasma
pS6	phosphorylated S6
PT	prothrombin time
PTEN	phosphatase and tensin homolog
PTT	partial thromboplastin time
QD	once daily
QLQ	quality of life questionnaire
QOL	quality of life
QLQ-C30	Quality of Life Questionnaire-Core 30
qRT-PCR	quantitative real-time polymerase chain reaction
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RP2D	recommended Phase II dose
RPPA	reverse phase protein array
RTK	receptor tyrosine kinase
S6RP	S6 ribosomal protein
SDV	source data verification
SEER	Surveillance, Epidemiology and End Results
SLNB	sentinel lymph node excisional biopsy
t_{max}	time to peak concentration
TNBC	triple-negative breast cancer
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

According to the Surveillance, Epidemiology and End Results (SEER) database, over 230,000 women were diagnosed with breast cancer and approximately 40,000 women died of breast cancer in 2013 in the United States (SEER 2013). The lifetime probability of developing invasive breast cancer in the United States and Europe is one in eight (Sasieni et al. 2011). Globally, breast cancer is the most common invasive malignancy with a prevalence of more than 1.3 million patients and a mortality rate of approximately 450,000 deaths per year (Jemal et al. 2011).

The treatment algorithm for patients with breast cancer is based on several considerations, for example, clinical factors and histopathology characteristics, including the presence or absence of human epidermal growth factor 2 (HER2) amplification, and hormone receptor status. Most breast cancers in the Western world (approximately 94–95% of patients in the U.S. and Europe) are diagnosed when the cancer is still confined to the breast, with or without locoregional lymph node spread (Sant et al. 2003; Howlader et al. 2011). At this stage (early breast cancer [EBC]), the disease is usually operable and can be treated surgically with curative intent.

Even with current optimum treatment, approximately 20–45% of patients with clinically localized disease at diagnosis relapse (EBCTCG 2011, 2012). Upon relapse, patients with metastatic disease have a median survival of approximately 24 months and a 5-year life expectancy of 18–23% in the U.S. and Europe (Sant et al. 2003; Howlader et al. 2011). Thus, there is a substantial need to improve treatment outcomes for patients with early breast cancer to delay/prevent future relapse.

1.1.1 Molecular Classification of Breast Cancer, Including Triple-Negative Breast Cancer

Breast cancer is a genetically heterogeneous and biologically diverse disease. The long recognized clinical and phenotypic differences have been shown to correlate with differences at the gene expression level (van't Veer et al. 2002). Molecular profiling of breast cancers using cDNA array technology showed that breast cancer can be further sub-classified into Luminal A and B subgroups (with high expression of estrogen receptor/progesterone receptor [ER/PgR]), basal-like, HER2-enriched, and normal-like. The basal-like subtype was so named because the expression pattern of this subtype mimics that of basal epithelial cells of other parts of the body and normal breast myo-epithelial cells. The molecular drivers underlying the pathogenesis of the basal-like subtype are not well-understood.

Approximately 80% of basal-like breast cancers lack immuno-staining for hormone receptors and HER2 and are thus often referred to as triple-negative breast cancer (TNBC); approximately 15% of breast cancers are classified as TNBC. TNBCs are more likely to exhibit an aggressive phenotype, including high genomic instability, rapid

proliferation rate, and tendency to become metastatic. Although TNBC may respond to chemotherapy, including taxanes, there are no approved targeted therapies for patients with this disease in the U.S. or Europe. Overall, the clinical outcome for patients with TNBC is poor, relative to other breast cancer subtypes; patients generally experience rapid clinical progression and poor survival. Additional clinically active agents are needed for early TNBC.

1.1.2 PI3K/Akt Signaling in Triple-Negative Cancer

Akt is the central node of the PI3K-Akt-mammalian target of rapamycin (mTOR) signaling axis and represents a major downstream effector of receptor tyrosine kinases (RTKs). Activation of the PI3K/Akt pathway results in essential cellular functions including cell survival, growth, and proliferation, which are properties that underlie human cancers. The PI3K/Akt pathway can be activated through loss of the tumor suppressor phosphatase and tensin homolog (PTEN) (Li et al. 1997), through activating mutations and/or amplifications in PIK3CA (Bachman et al. 2004), or through loss of the phosphatase inositol polyphosphate 4-phosphatase, type II (INPP4B) (Fedele et al.2010); all these events are frequently observed in TNBC.

As demonstrated by the TCGA study (Cancer Genome Atlas Network 2012), among the breast cancer subtypes, basal-like-/triple-negative breast cancer was associated with the highest activity of PI3K/Akt pathway signaling as demonstrated by DNA copy number/mutation analysis, reverse-phase phosphoproteomic analysis (RPPA) and by gene expression signature. Genetically, mutations in the PIK3CA gene are found in approximately 9% of basal-like breast cancers; in addition, PTEN and INPP4B gene losses occur in approximately one-third of samples as evaluated by DNA copy number changes. Furthermore, deficient expression of tumor suppressors PTEN and INPP4B was found in >one-third of the basal-like breast cancers. These alterations were associated with a higher degree of Akt pathway activation (as determined by pAKT and pS6 levels RPPA) in the basal subtype relative to other breast cancer subtypes. Inactivation of PTEN using tissue-specific gene knockout experiments drives the development of basal-like breast cancer in animal models (Dourdin et al. 2008; Saal et al. 2008). [redacted]). Given that the Akt pathway in TNBC is frequently activated (by PTEN-dependent and -independent mechanisms), inhibition of Akt represents a compelling and rational potential treatment strategy.

1.1.3 Akt Activation and Chemoresistance

Activation of Akt signaling (whether intrinsic or induced following chemotherapy) leads to chemoresistance across several cancer models, including breast cancer. One reported

mechanism of Akt-mediated chemoresistance, in response to genotoxic stress, is that DNA-dependent protein kinase and Akt can cross-regulate DNA repair via non-homologous end-joining (Toulany et al. 2008). Additionally, Akt activation can lead to abrogation of the G_1-S checkpoint (via MDM2 phosphorylation) and the G_2-M checkpoint (in part via Chk1 activation) (Xu et al. 2012). Taxanes and other chemotherapeutic agents can induce up–regulation of Akt in cancer cell lines via multiple proposed mechanisms, resulting in chemo-resistance (Winograd-Katz and Levitzki 2006). Thus, up–regulation of Akt signaling represents a potentially important survival pathway in response to genotoxic stress, and activation of Akt signaling following chemotherapy (including taxanes) may promote cell survival (Isakoff et al. 2005).

Several studies have shown that inhibition of the PI3K/Akt pathway in diverse cancers leads to radiosensitization and/or chemosensitization (Brognard et al. 2001, Wallin et al. 2010). In contrast, overexpression/activation of Akt across several tumor models leads to chemoresistance (Clark et al. 2002; Liu et al. 2007), including to paclitaxel (Isakoff et al. 2005). Given that up–regulation of Akt signaling may lead to chemoresistance, targeting TNBC with an Akt inhibitor in combination with chemotherapy may increase treatment efficacy.

1.1.4 Neoadjuvant Therapy for Breast Cancer

The use of neoadjuvant therapy for breast cancer has been studied in several large randomized trials that have compared neoadjuvant chemotherapy with standard adjuvant treatment (Mauriac et al. 1991; Scholl et al. 1994; Semiglazov et al. 1994; Powles et al. 1995; Fisher et al. 1997; Wolff et al. 2000). Neoadjuvant therapy results in similar rates of disease-free survival (DFS) or overall survival (OS) compared with adjuvant therapy. A meta-analysis of nine randomized studies comparing adjuvant with neoadjuvant systemic therapy for breast cancer showed no difference in rates of death, disease progression or disease recurrence based upon the timing of the systemic therapy (Mauri et al. 2005). Rather, the major role of neoadjuvant treatment historically has been to reduce the size of unresectable tumors, allowing surgery to be performed; for example for operable tumors, neoadjuvant treatment allows for greater conservation of the breast and a decreased need for mastectomy (Hortobagyi et al. 1988; Fisher et al. 1997; Mieog et al. 2007). Because neoadjuvant therapy has comparable efficacy and safety to adjuvant therapy, the concept of neoadjuvant therapy is now well-established option for patients with EBC.

Across multiple neoadjuvant trials, patients who achieve a pathological complete response (pCR; and especially pCR defined as no residual disease present in both the breast and axilla) have an improved prognosis compared with those who have residual invasive disease present in the surgical specimen after completion of preoperative therapy (non-pCR). For example, in National Surgical Adjuvant Breast and Bowel Project (NSABP studies B-18 and B-27, HRs for DFS for patients who achieved a pCR relative to those who did not were 0.47 and 0.49, respectively in the two trials; the HRs

for OS were 0.32 and 0.36, respectively (Rastogi et al. 2008). In addition, the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis was conducted in 2012, evaluating over 12,000 patients treated with neoadjuvant chemotherapy as part of clinical trials (Cortazar et al. 2012). The results confirm an association between pCR and both event-free survival (EFS: hazard ratio [HR] 0.48, 95% CI 0.43–0.54) and OS (HR 0.36, 0.31–0.42). The association between pathological complete response and long-term outcomes was especially strong in patients with triple-negative breast cancer (EFS: HR 0.24, 95% CI 0.18–0.33; OS: HR 0.16, 0.11–0.25). In addition to benefit in TNBC patients noted above in the Cortazar et al. (2012) meta-analysis, Liedtke et al. (2008) found that pCR rates were higher with neoadjuvant treatment in patients with TNBC compared with those with non-TNBC (22% versus 11%; $p = 0.034$). The prognosis for patients who experience a pCR is excellent, with less than 10% developing a distant recurrence at 5 years, and equivalent to that for patients with other breast cancer subtypes who experience a pCR. However, those patients with TNBC who do not experience a pCR with the same chemotherapy have a much poorer prognosis. Interestingly, evaluation of residual tissue from TNBC patients who do not achieve a pCR demonstrated mutations affecting the PI3K–Akt pathway were enriched in post–neoadjuvant chemotherapy tumors compared with pretreatment tumors, suggesting Akt pathway contributes to chemoresistance (Blako et al. 2014).

1.2 BACKGROUND ON IPATASERTIB

Ipatasertib (GDC-0068) is a novel, selective, ATP-competitive small molecule inhibitor of all three isoforms of the serine/threonine kinase Akt and is potent in nonclinical models, including tumors with loss of PTEN (PTEN-low, PTEN-null, or PTEN-mutated) or mutations of PIK3CA both in vitro and in vivo. Ipatasertib inhibits the kinase activity of Akt and suppresses the phosphorylation of its direct substrates, including PRAS40, and additional downstream targets, such as S6 ribosomal protein (S6RP), resulting in G_1 arrest and/or apoptosis in human cancer cells (Lin et al. 2012).

See the Ipatasertib Investigator's Brochure for additional details on nonclinical and clinical studies.

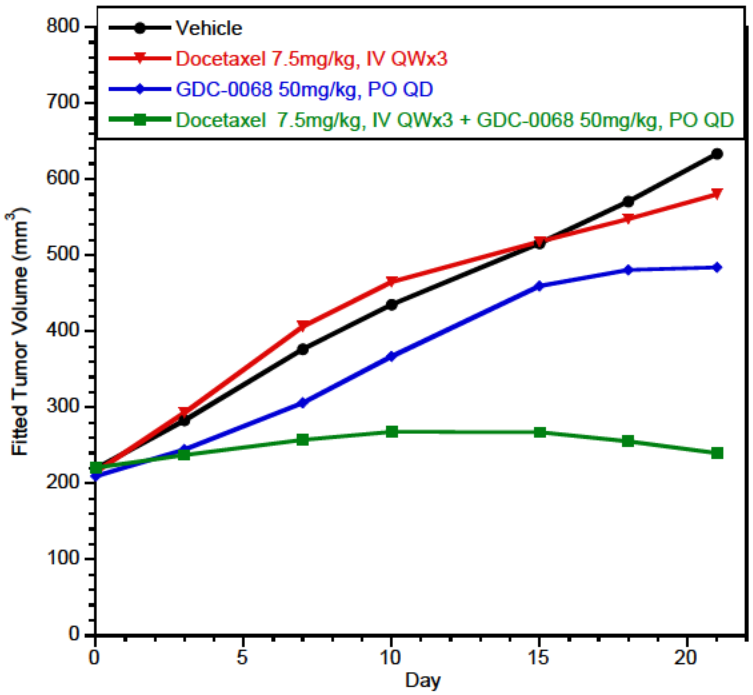
1.2.1 Summary of Ipatasertib Nonclinical Studies

Daily and intermittent dosing of ipatasertib has demonstrated tumor growth inhibition in nonclinical models of multiple tumors. In vitro studies showed that high levels of pAkt, often through inactivation of PTEN, predicted response to ipatasertib. [redacted] and the Ipatasertib Investigator's Brochure).

Ipatasertib and Taxane Nonclinical Combination Studies

The combination of ipatasertib with taxanes has been tested in several nonclinical models at Genentech. Incubation of a panel of cancer cell lines (including breast cancer lines) with taxane in the presence or absence of ipatasertib showed incremental cell inhibition with the addition of ipatasertib (GDC-0068; see the Ipatasertib Investigator's Brochure for further information). In a MCF7-neo/HER2 breast tumor xenograft model (HER2+, PIK3CA mutant), the combination of ipatasertib and a taxane produced greater tumor growth inhibition than either agent alone (see Figure 1). No significant differences in weight loss were observed in the different treatment groups.

Figure 1 Effect of Ipatasertib (GDC-0068) and Docetaxel on MCF7-Neo/HER2 Breast Tumor Xenografts in Nude Mice



IV=intravenous; PO=oral; QWx3=once a week dosing for 3 cycles; QD=once daily dosing.
Note: Ipatasertib (GDC-0068) was dosed 1 hour after docetaxel. Dose levels are expressed as freebase equivalents

1.2.2 Summary of Ipatasertib Clinical Studies

Ipatasertib is currently being tested as a single agent and in combination with chemotherapy, hormonal agents, or targeted agents in Phase I and Phase II clinical trials. See the Ipatasertib Investigator's Brochure for further details on all clinical trials with ipatasertib. Summaries of the clinical trials with ipatasertib as a single agent (Study PAM4743g) or in combination with chemotherapy (Study PAM4983g) are presented in the sections below.

1.2.2.1 Study PAM4743g—Phase I Study of Single-Agent Ipatasertib

Ipatasertib is currently tested in a Phase I open-label dose-escalation study (PAM4743g), in patients with refractory solid tumors, using a $3 + 3$ design to assess the safety, tolerability, and pharmacokinetics of ipatasertib administered orally once daily (QD) for 3 weeks, followed by a 1-week observation period. Ipatasertib was well tolerated in the first six cohorts (25, 50, 100, 200, 400, and 600 mg daily); 800 mg daily resulted in dose-limiting toxicity (DLT; fatigue and gastrointestinal intolerance). A patient in the expansion arm continues to receive treatment at an ipatasertib dose of 600 mg daily. No patients in the first six cohorts receiving 25 to 600 mg of ipatasertib experienced a DLT. The maximum tolerated dose (MTD) of ipatasertib was determined to be 600 mg orally QD on a 21-day-on and 7-day-off (21/7) schedule.

Study PAM4743g: Preliminary Safety Data

As of 31 March 2014, enrollment in Study PAM4743g was completed, with 52 patients enrolled and 51 patients treated with ipatasertib (GDC-0068), including 30 patients in the dose-escalation stage and 21 patients in the dose-expansion stage. The most frequently reported adverse events in $\geq 10\%$ of patients that were assessed by the investigators as related to ipatasertib were nausea (70.6%), diarrhea (68.6%), vomiting (51%), asthenia (37.3%), hyperglycemia (33.3%), decreased appetite (23.5%), dyspepsia (19.6%), dysgeusia (11.8%), rash (11.8%), and upper abdominal pain (11.8%). In the 800-mg cohort, 2 patients experienced a DLT of Grade 3 asthenia. No DLTs were reported in the 600-mg cohort; thus, 600 mg was determined to be the MTD on this schedule. Grade ≥ 3 adverse events in $\geq 5\%$ of patients that were assessed as related to ipatasertib were diarrhea ($n = 4$, 7.8%), and asthenia ($n = 3$, 5.9%). There were no ipatasertib–related Grade 4 or Grade 5 adverse events.

Study PAM4743g: Preliminary Pharmacokinetic Data

Pharmacokinetic (PK) data are available from 30 patients treated with ipatasertib during the dose-escalation stage from dose cohorts 1 to 7 (25 to 800 mg) on a 21/7 schedule, with PK data available from the single dose on Day 1 and following multiple doses (on Day 8 of continuous dosing). The preliminary PK profile of ipatasertib shows that ipatasertib is rapidly absorbed with time to peak concentration (t_{max}) ranging from 0.5 to 3 hours across all doses. The mean terminal half-life ranged from 21.7 to 31.4 hours at doses above 100 mg. Mean maximum concentration (C_{max}) and total exposure (area under the curve [AUC]) were dose-proportional in the range from 25 to 800 mg. Preliminary data also show that the pharmacokinetics of ipatasertib are comparable between the fed and fasted states. The transient increase in glucose and insulin are also comparable between the fed and fasted states of dosing following ipatasertib administration (for additional information, see the Ipatasertib Investigator's Brochure).

Study PAM4743g: Preliminary Pharmacodynamic Data

The pharmacodynamics of ipatasertib were assessed in Study PAM4743g on the basis of changes in the Akt pathway, including phosphorylated GSK3β (pGSK3β) in

platelet-rich plasma (PRP) and phosphorylated PRAS40 (pPRAS40) in predose and postdose tumor biopsies. GSK3β and PRAS40 are substrates of Akt (Yan et al. 2013). In PRP experiments, the pGSK3β level decreased by more than 60% at doses ≥200 mg and by more than 80% at the 600 mg dose, demonstrating a dose- and concentration-dependent pharmacologic response. Examination of multiple protein substrates of Akt in pre- and on-treatment tumor biopsies showed phosphorylation decreases of Akt pathway proteins, including more than 60% decrease in pPRAS40 (compared with baseline) in all three patients treated at 400 mg (see the Ipatasertib Investigator's Brochure for additional information).

1.2.2.2 Study PAM4983g—Phase Ib Study of Ipatasertib and Chemotherapy

Study PAM4983g is a Phase Ib, dose-escalation study, in patients with advanced solid tumors, to determine the MTD and recommended Phase II dose (RP2D) of ipatasertib administered QD orally in combination with docetaxel on a 14-day-on and 7-day-off (14/7) dosing schedule (Arm A), with mFOLFOX6 (Arm B; see the Ipatasertib Investigator's Brochure for details), and with paclitaxel (90 mg/m^2 administered weekly [3 week on and 1 week off]) with ipatasertib on a 21/7 dosing schedule (Arm C).

Study PAM4983g: Preliminary Safety Data for Ipatasertib + Taxanes in Arm A (Ipatasertib + Docetaxel) and Arm C (Ipatasertib + Paclitaxel)

As of 31 March 2014, enrollment in Study PAM4983g was completed for Arm A, with 27 patients enrolled in Arm A (ipatasertib combined with docetaxel), and enrollment was completed for Arm C, with 27 patients enrolled (ipatasertib combined with paclitaxel).

Ipatasertib in combination with docetaxel was well tolerated in the 27 patients in all dosing cohorts (100, 200, 400, and 600 mg); no patients receiving 100 to 600 mg of ipatasertib experienced a DLT. The adverse events reported in ≥10% of patients that were assessed by the investigators as related to ipatasertib (GDC-0068) in combination with docetaxel were nausea (74.1%), diarrhea (70.4%), vomiting (66.7%), decreased appetite (25.9%), asthenia (22.2%), fatigue (18.5%), dyspepsia (14.8%), hyperglycemia (14.8%), rash (14.8%), hypomagnesemia (11.1%), and mucosal Inflammation (11.1%). These adverse events were predominantly Grade 1 or 2. There were no ipatasertib-related Grade 4 or Grade 5 adverse events with the ipatasertib + docetaxel combination.

As of 31 March 2014, preliminary safety data from Study PAM4983g were available for 27 treated patients in Arm C (ipatasertib combined with paclitaxel 90 mg/m^2 administered weekly [3 week on and 1 week off]), including 21 patients treated at a 400 mg of ipatasertib and 6 patients treated at 600 mg of ipatasertib. No patients receiving ipatasertib in combination with paclitaxel experienced a DLT. The adverse events reported in ≥10% of patients that were assessed by the investigators as related to ipatasertib in combination with paclitaxel were diarrhea (77.8%), nausea (55.6%), vomiting (37%), fatigue (33.3%), decreased appetite (14.8%), rash maculo-papular

(14.8%), abdominal pain (11.1%), dehydration (11.1%), hyperglycemia (11.1%), and rash (11.1%). These adverse events were predominantly Grade 1 or 2. Grade 3 adverse events related to ipatasertib in combination with paclitaxel occurred mostly at 600 mg (in 5 of 6 patients or 83%), versus 400 mg of ipatasertib (in 3 of 21 patients or 14%), including diarrhea (n = 6), hyperglycemia (n = 3), dehydration (n = 2), anemia (n = 1), neutropenia (n = 1), and rash (n = 1). There were no Grade 4 or Grade 5 adverse events related to ipatasertib in combination with paclitaxel as assessed by the investigators. Three patients in the 600 mg ipatasertib + paclitaxel cohort were dose reduced for ipatasertib-related recurrent adverse events, including Grade 3 dehydration (n = 1), Grade 3 diarrhea (n = 1), and Grade 2 diarrhea (n = 1), while 1 patient in the 400 mg ipatasertib + paclitaxel cohort was dose reduced for ipatasertib-related Grade 1 iron-deficiency anemia. As of 31 March 2014, no patients in the 400 mg cohort had discontinued from the study for ipatasertib-related adverse events. In addition, no patients in the 400 mg cohort a had dose reduction or delay of paclitaxel due to ipatasertib-related adverse events.

As of 31 March 2014, 10 additional HER2-negative breast cancer patients enrolled in Arm C (400 mg ipatasertib +paclitaxel) of Study PAM4983g. All 10 patients completed Cycle 1 with no DLT, and the majority of the adverse events were Grade 1 and 2. The preliminary safety profile for this expansion cohort is consistent with that described above.

Based on the overall safety data from Arm C, the RP2D of ipatasertib is 400 mg daily on a 21/7 dosing schedule in combination with paclitaxel administered every 7 days.

Study PAM4983g: Preliminary Pharmacokinetic Data

As of 31 March 2014, preliminary PK data from Study PAM4983g were available for patients treated with ipatasertib combined with docetaxel (Arm A) or paclitaxel (Arm C). Ipatasertib exposures in both the docetaxel-treated and paclitaxel-treated arms were comparable to the Phase I single-agent data from Study PAM4743g. [redacted] and the Ipatasertib Investigator's Brochure).

Study PAM4983g: Preliminary Clinical Activity

As of 31 March 2014, 12 patients in Study PAM4983g had a radiographic response by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST, v1.1) criteria on computed tomography (CT) scans: 3 patients (11.1%) in Arm A (ipatasertib in combination with docetaxel), 3 patients (8.8%) in Arm B (ipatasertib in combination with mFOLFOX6), and 6 patients (22.2%) in Arm C (ipatasertib in combination with paclitaxel). All 3 patients in Arm A had previously received taxane (docetaxel or paclitaxel) chemotherapy, all 3 patients in Arm B had previously received FOLFOX or platinum (cisplatin or carboplatin) chemotherapy, and 4 of 6 patients in Arm C had previously received taxane (docetaxel or paclitaxel) chemotherapy. Molecular analysis

of archival tumor tissues is ongoing. At least 7 of the 12 patients (58%) with radiographic responses had tumors with alterations in the PI3K/Akt pathway, including low expression of PTEN (immunohistochemical H-score ≤200), PIK3CA mutations (E545K or H1047R), and 1 patient with an AKT1 E17K mutation (site information).

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

An estimated 1.3 million cases of breast cancer are diagnosed annually worldwide. Of these, approximately 200,000 are of the triple-negative (ER–/PR–/HER2–) phenotype. Improving the results of chemotherapy when the disease is still localized to the breast and regional lymph nodes offers the chance of potentially curing the disease, as well as delaying disease recurrence and death in those who are not cured. In neoadjuvant setting, pCR correlates with a favorable outcome in TNBC; thus pCR is a useful tool to enable rapid and effective evaluation of much needed new targets and treatments for TNBC. Evaluation of residual tissue from TNBC patients who do not achieve a pCR demonstrated mutations affecting the PI3K–Akt pathway were enriched in post-neoadjuvant chemotherapy tumors compared with pretreatment tumors, suggesting activation of the Akt pathway contributes to chemoresistance (Blako et al. 2014).

As demonstrated by the TCGA study (Cancer Genome Atlas Network 2012), TNBC often exhibits activation of PI3K/Akt signaling, relative to other breast cancer subtypes. For example, >50% of patients with TNBC exhibit low RNA expression of INPP4B and/or increased expression of AKT3. [redacted] Ipatasertib Investigator's Brochure).

Clinical safety profile of ipatasertib as a single-agent in the Phase Ia study (PAM4743g) and in combination with paclitaxel in the Phase Ib study (PAM4983g) supports development in breast cancer. As a single-agent, ipatasertib has a predictable PK profile with a half-life of approximately 24 hours, and ipatasertib significantly downregulates the PI3K/Akt pathway at doses ≥200 mg. In the Phase Ib study (PAM4983g), ipatasertib 400 mg daily was well-tolerated when combined with paclitaxel, exhibiting primarily Grade 1 to 2 gastrointestinal adverse events (e.g., nausea, vomiting, and diarrhea) and did not exacerbate the known adverse events attributable to paclitaxel.

The study population eligible for this trial is at high risk for relapse (≥20% over 5 years); the addition of effective and tolerable therapy to conventional neoadjuvant regimen may increase pCR rates and thereby improve longer-term outcomes for these patients. In addition, there may be additional benefits such as improved chances of breast-conserving surgery (BCS) in patients who desire this, and reduced rates of

re-operation for residual disease following primary surgery. The addition of ipatasertib to taxane-based neoadjuvant regimen is expected to be generally well tolerated. Significant increases in leukopenia, febrile neutropenia, or cardiac toxicity are not anticipated but will be monitored during the trial. Given the data to date, the benefit-risk assessment for administration of ipatasertib as part of a neoadjuvant treatment regimen within this clinical trial is considered positive.

Given that activation of the PI3K/Akt pathway is frequent in TNBC and may lead to chemoresistance, and ipatasertib can be safely combined with paclitaxel, this Phase II trial is designed to test the hypothesis that inhibition of PI3K/Akt signaling will enhance the efficacy of paclitaxel chemotherapy in the neoadjuvant treatment of patients with TNBC. The primary endpoint of this study will estimate the magnitude of benefit via pathologic complete response (pCR) in the breast and axilla of ipatasertib in combination with paclitaxel for patients with TNBC, as well as to prospectively evaluate whether patients whose tumors harbor a low/absent PTEN expression (by IHC) derive greater benefit from this regimen relative to the overall intent-to-treat population. Other hypothesis generating exploratory analyses will be conducted as appropriate to evaluate molecular signatures that could predict patient response.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is to estimate the efficacy of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in patients with early stage TNBC, as measured by local pathology laboratory evaluation of pCR rate within the breast and axilla (ypT0/Tis ypN0) in all patients and in patients with PTEN-low tumors.

The secondary efficacy objectives for this study are as follows:

- To estimate the clinical activity of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel, as measured by local pathology laboratory evaluations of pCR within the breast (ypT0/Tis) in all patients and in patients with PTEN-low tumors
- To evaluate objective response rate (ORR) assessed by breast MRI via modified Response Evaluation Criteria in Solid Tumors (RECIST) of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in all patients and in patients with PTEN-low tumors
- To estimate the clinical activity, as measured by pCR (ypT0/Tis and ypT0/Tis ypN0) and ORR of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in patients who are Akt diagnostic positive (Dx+) (defined by PTEN status, INPP4B status, and PI3K alterations) (see Section 4.5.1.7)

- To assess pCR rates according to subtypes of breast cancer defined by molecular profiles (e.g., the intrinsic subtypes of breast cancer defined by the PAM50 classifier)
- To assess the rates of BCS and conversion to BCS of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in women with T2 or T3 tumors

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of ipatasertib combined with paclitaxel versus placebo combined with paclitaxel.

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of GDC-0068 using a sparse sampling methodology, when given in combination with paclitaxel in early stage TNBC patients.

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To assess the effect of PI3K/Akt pathway alterations on pCR in patients treated with ipatasertib combined with paclitaxel versus placebo combined with paclitaxel, based on exploratory analysis of tumor tissue using molecular data obtained by one or more of the following analyses:

  Mutation and RNA/DNA copy number changes in oncogenes, tumor suppressors, and/or other genes associated with TNBC response to treatment and progression by DNA sequencing and/or in situ hybridization (ISH)

  Levels of Akt pathway proteins, as evaluated by RPPA

  Levels of tumor suppressors and/or RTKs by IHC
- To evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess the exposure-response relationships for efficacy, safety, and biomarker data

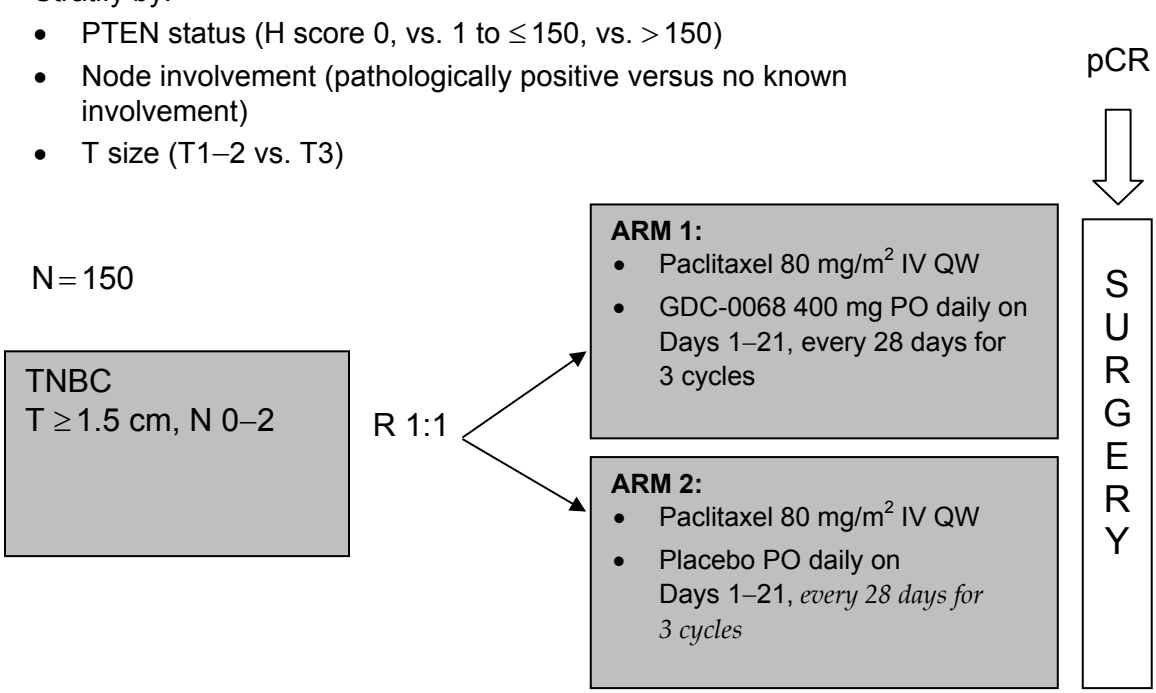
3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a randomized, double-blind, placebo-controlled, multicenter, pre-operative Phase II study designed to estimate the efficacy of ipatasertib combined with paclitaxel chemotherapy versus placebo combined with paclitaxel chemotherapy in women with Stage Ia–IIIa (primary tumors ≥ 1.5 cm) triple-negative breast adenocarcinoma. Patients with cT4 or cN3 tumors are not eligible. Patients and investigators will be blinded to study treatment. ER- and PgR-negative is defined as $< 1\%$ of tumor cell expression of

ER and PgR. Patients who have an unknown ER, PgR, or HER2 status and for whom determination of status is not possible are also not eligible for this study. Estimated benefit will be compared in all patients (independent of results from the diagnostic assessments of the tumor) and in patients with PTEN-low tumors. The study schema is shown in Figure 2.

Figure 2 Study Schema



IV = intravenous; PO = orally; QD = once daily; QW = once weekly.

Approximately 150 patients will be enrolled at approximately 30 centers. Patients will be randomized in a 1:1 ratio, stratified by the following three factors: PTEN status (H score 0, vs. 1 to ≤150, vs. >150), node involvement (pathologically positive versus no known involvement), and T size (T1–2 vs. T3).

For the purpose of enrollment, ER, PgR, and HER2 will be locally determined prior to beginning of study treatment. Additionally, all enrolled patients must consent to provide sufficient and evaluable archival tissue for PTEN status determination. In the absence of archival tissue, fresh tissue biopsy samples, excluding cytology and fine-needle aspiration (FNA) specimens, will be acceptable; however, evaluation of the patient's tumor sample for PTEN status by a central laboratory should occur prior to the initiation of study treatment. All patients will undergo pretreatment tumor tissue acquisition (snap-frozen, optimal cutting temperature [OCT], and formalin-fixed paraffin-embedded [FFPE] cores). One pretreatment FFPE core biopsy and two freshly frozen core

biopsies must be obtained for all patients prior to initiating study treatment. Pre-surgical FNA or core biopsy of suspicious node is allowed, but full excision lymph node biopsy (e.g., sentinel lymph node excisional biopsy [SLNB]) is not allowed.

All patients will receive paclitaxel 80 mg/m^2 (see Table 1 for regimen and dose adjustments) every 7 days for a total of 12 doses *(i.e., Days 1, 8, 15, and 22 of each cycle)*. Patients in the experimental arm will receive ipatasertib at a dose of 400 mg administered orally QD on Days 1 to 21 every 28 days and those in the control arm will receive placebo on the same days. Each cycle will be 28 days in duration and study treatment will continue for a total of three cycles until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination. Following three cycles of treatment, patients will undergo surgery.

Prior to administration of the second paclitaxel dose, a second research biopsy will be conducted for biomarker evaluation; at least one FFPE and at least two frozen OCT cores biopsy samples will be obtained.

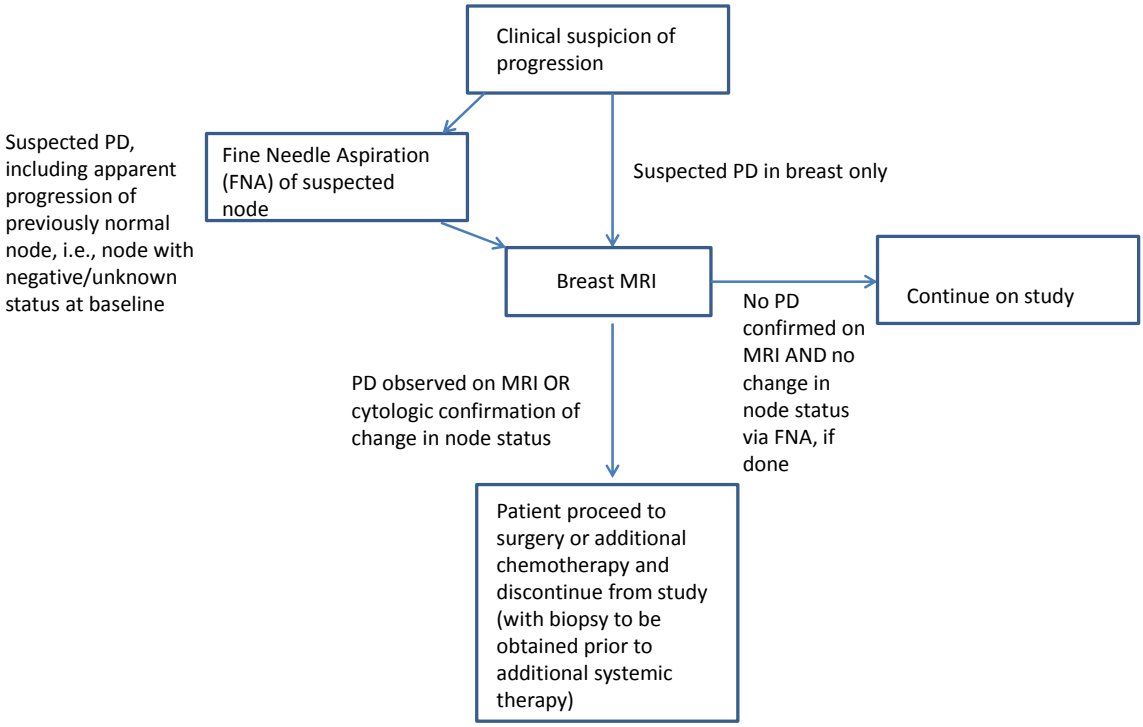
Primary breast tumor and axillary lymph nodes will be assessed every 4 weeks until Week 13 by clinical breast exam (palpation and clinical measurement; caliper preferred). Suspicion of progression based on clinical exam should be further evaluated (see Figure 3). Tumor measurement by MRI for disease evaluation will be performed at screening and prior to surgery (at approximately Weeks 10–12, following completion of neoadjuvant chemotherapy). Early assessment by MRI is allowed for suspected progression. Estimation of ORR will be by modified RECIST (see Appendix 3).

Patients with clinical or radiologic evidence of significant residual or progressive disease, as defined by modified RECIST, can either proceed directly to surgery or be discontinued from the study based on the investigator's discretion. Patients who discontinue study treatment prior to surgery will be required to have an additional research biopsy where at least one FFPE and at least two frozen OCT core biopsy samples will be obtained.

Safety will be evaluated during the study through the monitoring of all serious and nonserious adverse events, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE, v4.0).

The pharmacokinetics of ipatasertib/placebo will be assessed in all patients.

Figure 3 Evaluation of Clinical Suspicion of Progression or Significant Residual Disease



FNA = fine-needle aspiration; MRI = magnetic resonance imaging; PD = progressive disease.

During Weeks 10–12 (approximately; i.e., near the time of completion of neoadjuvant chemotherapy), the patient will consult with the surgeon to plan the type of breast surgery to be performed (breast conservative vs. mastectomy) and to schedule the date for surgery (see Section 3.1.1).

Following surgical resection of primary tumor, patients are expected to continue post-operative treatment with a standard adjuvant chemotherapy regimen such as 5-FU/doxorubicin/cyclophosphamide (FAC), 5-FU/epirubicin/cyclophosphamide (FEC), or doxorubicin/cyclophosphamide (AC), if appropriate and as chosen by their treating physician. Post-operative treatment information (chemotherapy, radiotherapy, etc.) will be collected at the post-surgery visit.

The primary efficacy endpoint, pCR within the breast and axilla (ypT0/Tis ypN0) in all patients and in patients with PTEN-low tumors will be assessed by local pathology evaluation following completion of neoadjuvant therapy and surgery.

The trial is anticipated to have a recruitment period of approximately 24 months.

A schedule of assessments is provided in Appendix 1.

3.1.1 Surgery

The patient should be evaluated at baseline and during approximately Weeks 10–12 of treatment to plan the surgical procedure (BCS or mastectomy); both the physician recommendation and final patient decision should be documented in the electronic Case Report Form (eCRF).

Surgery will take place no more than 5 weeks after the last dose of paclitaxel. Breast and axillary surgery will follow local practice. However, pre-surgical SLNB is not allowed. Information on the type of surgery will be collected and recorded. Representative surgery specimens will be sent to a central laboratory for assessment of Akt pathway markers.

Following surgery, patients are expected to continue post-operative treatment according to local and institutional standards, including the use of adjuvant chemotherapy.

A post-surgery visit will be performed within approximately 4 weeks after surgery for assessment of adverse events and general safety. In addition, follow-up adjuvant chemotherapy and radiation therapy should be recorded, once known, in the eCRF.

3.1.2 Joint Monitoring Committee

A Joint Monitoring Committee (JMC) will be in place during the study and will provide oversight of safety and efficacy. The primary responsibility of the JMC is to review the available safety data and to make a recommendation to continue, modify the study design as required for improved safety, or terminate the study. *While a JMC review is being conducted, patient accrual into the study will continue.* The JMC will be composed of a designated sponsor medical oncologist (who is not the study medical monitor), the drug safety officer, and the study biostatistician. In addition, *the* JMC will also include at least two external medical oncologists who are not employees of Roche/Genentech and are not affiliated with the study team, to provide clinical and methodological expertise in early breast cancer. The members of the JMC will not interact with the sites or investigators in terms of study conduct.

The reviews the JMC will conduct are described in Section 6.8.1 and Section 6.8.2.

3.2 END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) 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. LPLV is expected to occur approximately 7 months after the last patient is enrolled.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Conducting the Study in the Neoadjuvant Setting

Neoadjuvant therapy, a systemic therapy administered prior to breast cancer surgery, has become an increasingly popular approach in the systemic treatment of early breast cancer patients. Outcomes of patients receiving neoadjuvant therapy have been shown to be equivalent to those of adjuvant therapy (Mauri et al. 2005), and the former offers clear advantages to patients, particularly for patients with larger tumors; patients with smaller breast tumors (1–2 cm) also have been shown to benefit. Tumor shrinkage prior to surgery may allow breast conservation surgery (Coudert et al. 2006), and since the response to therapy can be monitored, the patient might be also spared further treatment with inactive medications. Upon completion of neoadjuvant treatment and surgery, patients are expected to continue to receive further adjuvant therapy (e.g., radiation and additional chemotherapy), if appropriate, following discussion with the treating physician.

The neoadjuvant setting provides a unique opportunity to identify predictive biomarkers of response to novel therapeutic agents. Pretreatment biopsies are easily accessible, usually from the diagnostic specimens. On-treatment biopsies may also be pre-specified in order to monitor pharmacodynamic markers of treatment response at a biological level. Finally, the surgical specimen, if pCR is not reached, can be utilized as well to understand mechanisms of resistance. The biological information obtained from all these biological specimens can be correlated with clinical data, such as pCR, a surrogate endpoint that demonstrates strong association with disease-free and overall patient survival in some subtypes of breast cancer (Cortazar et al. 2012; von Minckwitz and Fontanella 2013).

Of note, at the completion of study treatment in this study, patients are expected to continue post-operative treatment with a standard anthracycline-based chemotherapy regimen such as FAC, FEC, or AC. The specific regimen will be chosen by the treating physician per local guideline, and should be recorded in the eCRF.

3.3.2 Rationale for Starting Dose and Schedule of Ipatasertib

For ipatasertib, the starting dose of 400 mg QD and the starting schedule of 21 days on and 7 days off (21/7) were selected on the basis of safety data from Arm C of Study PAM4983g, the Phase Ib trial of ipatasertib combined with paclitaxel (see Section 1.2.2.2). In Arm C of Study PAM4983g, ipatasertib was generally well tolerated when administered at a dose of 400 mg QD on a 21/7 dosing schedule, in combination with paclitaxel 90 mg/m^2 administered weekly (3 week on and 1 week off). A relative bioavailability study (Study GP29066) has been conducted in healthy volunteers and showed that 400-mg tablet dose of ipatasertib to be used in this study will provide exposures similar to the Phase II 400-mg dose of ipatasertib in the capsule formulation used in Study PAM4983g.

3.3.3 Rationale for Treatment with Paclitaxel and Choice of Paclitaxel Regimen

No globally accepted standard treatment exists specifically for neoadjuvant TNBC; rather, widely divergent chemotherapy followed by surgery (and radiation therapy) remain the cornerstone of treatment. The role of paclitaxel in the treatment of breast cancer has been well established in both the adjuvant and metastatic settings. Multiple trials demonstrated an increase in DFS in breast cancer patients who received paclitaxel-based therapy in the adjuvant setting (Hayes et al. 2007; Mackey et al 2013). In addition, taxanes are among the most active chemotherapy agents for the treatment of MBC in terms of response rates or survival, based on a meta-analysis of three randomized trials comparing a taxane with an anthracycline (Piccart-Gebhart et al. 2008). The pCR response rate of single agent paclitaxel is approximately 15–25% for TNBC patients treated in the neoadjuvant setting (Llombart et al. 2012); this pCR rate with paclitaxel is comparable to pCR in large single institution studies across diverse regimens (Ju et al. 2012). Two Phase III studies showed that addition of bevacizumab results in a modest increase in pCR, particularly in patients with TNBC; however the addition of bevacizumab did not alter rate of BCS and was associated with increased Grades 3 and 4 toxicity and treatment discontinuation. The role of adding platinum therapy to standard neoadjuvant regimen has recently been tested in GeparSixto and Cancer and Leukemia Group B (CALGB) 40603 trials (Sikov et al. 2013; von Minckwitz et al. 2014). These trials also showed that although the addition of platinum resulted in improvement in pCR, there were substantial hematologic and other toxicities, leading to dose reductions and early treatment discontinuations. It is unknown at this time whether the modest improvement in pCR observed in these trials (10–15%) will result in improved DFS or OS. Paclitaxel results in reasonable pCR rate with manageable adverse event profile, allowing completion of the neoadjuvant treatment course and is thus a widely used and appropriate therapy for patients treated in this setting.

Dose and regimen for paclitaxel in neoadjuvant and metastatic setting has been tested in several clinical trials. In the neoadjuvant setting, weekly paclitaxel was also shown to improve the likelihood of pathologic complete remission in the breast and axillary lymph nodes (28.2% vs. 15.7%; $p = 0.02$), as well as the opportunity for BCS ($p = 0.02$), when compared with paclitaxel administered every 3 weeks in the neo-adjuvant setting (Green et al. 2005). In the metastatic setting, results of the CALGB 9840 showed that paclitaxel 80 mg/m^2 administered weekly had superior efficacy to and was better tolerated than paclitaxel 175 mg/m^2 administered every 3 weeks in patients with MBC (Seidman et al. 2004). This Phase II study (GO29505) will use a similar regimen of paclitaxel 80 mg/m^2 administered weekly that was tested in the above referenced trials, as well as that used in the SOLTI NeoPARP trial (NCT01204125).

Upon completion of study treatment in this study, patients are expected to continue post-operative treatment with a standard anthracycline-based chemotherapy regimen

such as FAC, FEC, or AC. The specific regimen will be chosen by the treating physician per local guidelines, and should be recorded on the eCRF.

3.3.4 Rationale for Objective Response Assessed by MRI and Inclusion of Other MRI-Derived Metrics for Exploratory Purposes

ORR is based on criteria related to changes in tumor size (e.g., RECIST) and is generally defined as the sum of partial and complete responses. ORR is a robust indicator of antitumor activity in new anticancer agents and is considered to be an established surrogate marker for clinical benefit. It has been used as a primary endpoint in multiple neoadjuvant trials (Smith et al. 2005; Ellis and Ma 2007; Baselga et al. 2009).

Guidelines for RECIST 1.1 state that MRI is the preferred modality to follow breast lesions in a neoadjuvant setting, and it has advantages over CT and mammography (Eisenhauer et al. 2009). In addition, MRI has been shown to be more accurate than clinical palpation, ultrasound, and mammography for measuring residual tumor size after neoadjuvant therapy in several prospective trials (Balu-Maestro et al. 2002; Yeh et al. 2005; Akazawa et al. 2006), including the I-SPY trial (Hylton et al. 2012).

Results from the I-SPY trial also showed that tumor volume measurements based on the percent of tumor with enhancing signal after MR contrast agent administration may be a more sensitive measure of response during neoadjuvant treatment than longest dimension measures. Enhancing tumor volume, along with other MRI-derived metrics acquired within the same MRI exam such as the apparent diffusion coefficient (ADC; a measure of tumor cellular composition derived from diffusion-weighted imaging), (Partridge et al. 2013), may serve as additional prognostic and/or predictive biomarkers of neoadjuvant therapy.

3.3.5 Rationale for Collection Tissue for Examining PTEN and Other AKT Pathway Components as Diagnostic Biomarkers

Akt pathway activation in tumors, as demonstrated by PTEN loss, INPP4B loss, PIK3CA mutations, etc., may be an important predictive diagnostic for efficacy of ipatasertib. PTEN loss is an important cause of constitutively active Akt, and represents a potentially important predictive biomarker. Activation of PI3K/Akt signaling frequently occurs in TNBCs; approximately 60% of TNBC samples exhibit low expression of PTEN. In this Phase II study, PTEN status will be performed prospectively from archival tissue (or fresh biopsy if archival is not available), and the results will be used to stratify patients in this study.

[redacted] Activation of the Akt results in increased levels of phosphorylated down-stream effector proteins, including pPRAS40,

pS6, pGSK3b; these proteins can be evaluated by IHC and/or reverse phase protein array from archival and/or fresh biopsy samples. Collectively, these data could elucidate if the detection of alterations in the PI3K/Akt pathway, including low PTEN expression, loss of INPP4B activity, activating mutation in PIK3CA, and/or AKT3 overexpression, can be used to identify patients who may especially benefit from the combination of ipatasertib with paclitaxel.

Taken together, these considerations support the collection of tissue from patients to evaluate the activity of ipatasertib combined with paclitaxel in patients with early TNBC in order to assess the clinical impact of these biomarkers.

3.3.6 Rationale for Collection of Fresh Tumor Biopsies Following Progression for Exploratory Purposes

Exploratory assessments of biologic markers will be performed. If tumor biopsies can be obtained with minimal risk and discomfort to patients who progressed during therapy, tissue may be collected at the end of the study (e.g., following disease progression prior to start of next therapy) from patients who consent to this procedure. Tissue samples will be assessed for alterations in the PI3K/Akt pathway, as this may help predict which patients may benefit from ipatasertib and may also help identify potential causes of acquired resistance to ipatasertib. Tumor biopsies may be used to explore PI3K/Akt pathway marker levels, gene copy number changes, and mutations to evaluate potential mechanisms of resistance to the combination of ipatasertib and paclitaxel.

3.3.7 Rationale for Collection of Blood Samples for Noninvasive Disease Monitoring

Circulating tumor DNA (ctDNA) can be detected in the blood of cancer patients with epithelial cancers and may have diagnostic and therapeutic significance (Schwarzenbach et al. 2011). For example, the mutational status of tumor cells may be obtained through the isolation of ctDNA (Maheswaran et al. 2008), and ctDNA has been used to monitor treatment effectiveness in melanoma, as well as in breast cancer (Shinozaki et al. 2007). An assay has been developed to identify major mutations in the PIK3CA gene through analysis of ctDNA in plasma. In this study, blood samples will be collected at screening and during the study to evaluate oncogenic mutations at baseline and to assess for possible emergence of new mutations after treatment with ipatasertib and paclitaxel. Mutations will be evaluated in relevant genes in the PI3K/Akt pathway, including but not limited to PIK3CA. It is estimated that up to 10% of TNBCs may harbor PIK3CA mutations (Zang et al. 2012). Identifying potential discordances in the PIK3CA status from baseline to post-surgery/end-of-study through exploratory analysis of archival tumor samples and ctDNA may help clarify the prognostic and predictive significance of PIK3CA mutations in patients with TNBC treated with ipatasertib and paclitaxel.

3.3.8 Rationale for the Pharmacokinetic Evaluation Schedule

A sparse sampling strategy will be applied in this study (see Appendix 2 for schedule). The sampling schedule is designed to enable characterization of GDC-0068 PK following first dose and at steady-state using population PK methodology (PopPK). In addition, the PK data will allow comparison to single agent GDC-0068 PK data from the single agent Phase Ia Study PAM4743g and to combination data with paclitaxel from the Phase Ib Study PAM4983g. Individual PK parameters estimated from the sparse sampling scheme will be used for exploratory exposure-response analyses.

Paclitaxel concentrations will not be measured as a PK interaction between GDC-0068 and paclitaxel is not expected, based on results from Study PAM4983g.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The primary efficacy outcome measure in all patients and in patients who have PTEN-low tumors is as follows:

- pCR rate in breast and axilla as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system by local pathology evaluation.

The secondary efficacy outcome measures in all patients and in patients who have PTEN-low tumors or who are Akt Dx+, are as follows:

- Objective tumor response by MRI, as assessed by the investigator per modified RECIST (see Appendix 2)
- pCR rate in breast as defined by ypT0/Tis in the American Joint Committee on Cancer staging system by local pathology evaluation
- Comparison of the rates of BCS and conversion to BCS in patients with T2 or T3 tumors

3.4.2 Safety Outcome Measures

The safety and tolerability of ipatasertib when combined with paclitaxel will be assessed using the following outcome measures:

- Incidence, nature, and severity of adverse events, graded according to the NCI CTCAE, v4.0
- Clinically significant changes in vital signs, physical findings, and clinical laboratory results during and following ipatasertib administration

3.4.3 Pharmacokinetic Outcome Measures

For ipatasertib, the following PK parameters will be analyzed using a PopPK approach as data allow:

- Exposure following first dose (AUC_{0-24}) and steady-state (AUC_{ss})
- Minimum observed plasma concentration (C_{min}; trough concentration)

- Apparent clearance following oral dosing (CL/F)

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Alterations in DNA and RNA, including but not limited to mutational status, RNA expression levels, DNA copy number, protein expression and modifications
- Evaluation of changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluation of changes in tumor cellular composition as assessed by diffusion-weighted MRI

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with early stage (Stage Ia–IIIa; primary tumors ≥ 1.5 cm) triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for this breast cancer may be eligible for this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Premenopausal or postmenopausal women, age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 4)
- Histologically documented triple-negative carcinoma of the breast with all of the following characteristics:

  Primary tumor ≥ 1.5 cm in largest diameter (cT1–3) by MRI. In the case of a multifocal tumor (defined as the presence of two or more foci of cancer within the same breast quadrant), the largest lesion must be ≥ 1.5 cm and designated as the “index” lesion for all subsequent tumor evaluations.

  Stage I to operable Stage IIIa breast cancer
- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for PTEN status by central histopathology laboratory

  Specimen may consist of a tissue block (preferred) or 10 unstained, serial slides. Cytologic or FNA samples are not acceptable.

  If archival tissue is either insufficient or unavailable, FFPE core sample from a pretreatment biopsy of the tumor may be used.

  Cytologic or FNA samples are not acceptable.
- Adequate hematologic and organ function within 14 days before the first study treatment, defined by the following:

  Neutrophils (absolute neutrophil count [ANC] ≥ 1500/μL)

Hemoglobin ≥ 9 g/dL

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

Serum albumin ≥ 2.5 g/dL

Total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN) with the following exception:

Patients with known Gilbert's disease who have serum bilirubin $\leq 3 \times$ ULN may be enrolled

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.0 \times$ ULN

Alkaline phosphatase $\leq 2 \times$ ULN

Partial thromboplastin time (PTT) and/or either international normalized ratio (INR) or prothrombin time (PT) $\leq 1.5 \times$ ULN (except for patients receiving anticoagulation therapy).

Patients receiving heparin treatment should have an activated partial prothrombin time (aPTT) between 1.5 to $2.5 \times$ ULN (or patient value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 to 4 days apart.

Fasting serum glucose ≤ 150 mg/dL (8.33 mmol/L) and HbA1C $\leq 8\%$

- Able to comply with the study protocol, in the investigator's judgment
- For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 6 months after the last dose of study drug

  Abstinence is acceptable only if it is in line with 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.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include tubal ligation, male sterilization, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $< 1\%$ per year. Barrier methods must always be supplemented with the use of a spermicide.

4.1.2 Exclusion Criteria

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

- Known HER2-positive, ER-positive, or PgR-positive breast cancer

  HER2 positivity is defined as one of the following: On IHC testing, $> 10\%$ of contiguous and homogeneous tumor cells show protein overexpression (IHC 3+) or on ISH testing, or gene amplification (HER2 copy number or HER2/CEP17 ratio by ISH based on counting at least 20 cells within the area). If results are

equivocal, reflex testing should be performed using an alternative assay (IHC or ISH).

ER and PgR positive are defined as $\geq$1% of cells expressing hormonal receptors via IHC analysis.

Patients who have not had HER2, ER, or PgR testing, and thus, the HER2, ER, and PgR status of the breast adenocarcinoma is unknown, are not eligible.

- Any prior treatment for the current primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer (Note: Staging exams are at the discretion of the investigator).
- Bilateral invasive breast cancer
- Multicentric breast cancer (the presence of more than one tumor in different quadrants of the breast)
- Patients who have undergone excisional biopsy of primary tumor and/or axillary lymph nodes
- Patients who have undergone excisional SLNB prior to study treatment

  Pre-surgical FNA or core biopsy of suspicious node is allowed.
- Any contraindication to MRI examination, including the following:

  Neurostimulators

  Pacemakers

  Implanted metallic material or devices (metal implants or large tattoos in the field of view)

  Severe claustrophobia

  Physical characteristics (weight and/or size) that exceed the capabilities of the MRI scanner

  Known allergy or hypersensitivity reactions to gadolinium, versetamide, or any of the inert ingredients in gadolinium-based contrast agents

  Severe renal insufficiency, e.g., estimated glomerular filtration rate $<$30 mL/min
- Need for chronic corticosteroid therapy of $\geq$20 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Known hypersensitivity or contraindication to any component of the study treatments, including paclitaxel excipient macrogolglycerol ricinoleate
- Grade $\geq$2 peripheral neuropathy
- History of Type I or Type II diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication $\geq$2 weeks prior to initiation of study treatment are eligible for enrollment

- New York Heart Association (NYHA) Class II, III, or IV heart failure (see Appendix 5) or left ventricular ejection fraction $<50\%$, or active ventricular arrhythmia requiring medication
- Current unstable angina or history of myocardial infarction within 6 months prior to Cycle 1, Day 1
- Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- Congenital long QT syndrome or screening corrected QT interval (QTc) >480 milliseconds
- History of malabsorption syndrome, lack of physical integrity of the upper gastrointestinal tract, or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Active infection requiring intravenous (IV) antibiotics
- Known HIV infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., Hepatitis B or Hepatitis C virus), current alcohol abuse, or cirrhosis
- Pregnant or lactating, or intending to become pregnant during the study

  Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Malignancies other than TNBC within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, ductal carcinoma in situ treated surgically with curative intent); medical monitor will make final determination for cancers not mentioned here.
- Active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis)
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained, the study site will obtain the patient's screening number from the Interactive Web Response System (IWRS). Once eligibility has been established, the patient will be enrolled, and the study site will obtain the patient's identification number from the IWRS.

The patient will be randomized, and the site will obtain the blinded study drug kit number from the IWRS.

4.2.1 Study Patients and Analysis Groups

This study is a randomized, double-blind, placebo-controlled, multicenter, clinical trial designed to estimate the effect on pCR of the addition of ipatasertib to paclitaxel (Arm 1) compared with placebo plus paclitaxel (Arm 2). This comparison (Arm 1 vs. Arm 2) will be performed in all patients (independent of results from the diagnostic assessments of the tumor) and in specific subsets of patients with PTEN-low tumors (see Section 6.4) to estimate the clinical effect of PTEN status and to provide information for the design of future confirmatory studies.

4.2.2 Control Groups

All patients will receive paclitaxel chemotherapy for the treatment of triple-negative breast adenocarcinoma and will receive either QD dosing of ipatasertib or a placebo control. A placebo will be used to maintain treatment blinding and will be formulated to appear identical to ipatasertib but will not contain any active ingredient.

4.2.3 Minimization of Bias

Patients will be allocated to each of the treatment arms (Arm 1 or Arm 2) through the use of a stratified permuted block randomization to ensure within-stratum balance of patient characteristics between treatment arms. Randomization will be stratified by the following three factors: PTEN status (H score 0, vs. 1 to $\leq$150, vs. $>$150), Node involvement (pathologically positive versus no known involvement), and T size (T1-2 vs. T3). These three stratification factors were chosen because of their known or suspected prognostic value and/or potential to affect efficacy of paclitaxel with/without ipatasertib. Prospective stratification by these factors will minimize differences in the two treatment arms as a result of sources other than ipatasertib.

Placebo tablets will be identical in shape and in color to the ipatasertib tablets and will be undistinguishable (see Section 4.3.1.1 for details). Tablet bottles and drug kits for placebo will also be identical to those for ipatasertib, except for the unique kit numbers on the kit boxes.

To minimize bias from potential unblinding, an IWRS provider will conduct randomization and hold treatment assignment codes.

Because of the size of the study, use of IWRS, randomization, blinding, and expected lack of substantial emergency unblinding, collected data will be protected from any biases that would arise from subjectivity in the reporting of the outcome measures. To further protect the integrity of the study, the results of interim safety and efficacy analyses will not be made known to the investigators, and the PTEN loss status or other AKT pathway alterations within the tumor samples will not be disclosed to the investigators.

The addition of ipatasertib to paclitaxel is not expected to affect planned laboratory tests or adverse reactions to a degree that would significantly unblind patients or investigators.

All laboratory tests of blood specimens will be performed by a local laboratory, a central laboratory, or the Sponsor, as appropriate. To maintain blinding, patient-specific plasma concentration data for ipatasertib will not be made known to either investigators or the contract research organizations (CROs).

The investigator and the patient will be blinded to treatment assignment.

4.2.4 Method of Unblinding

Emergency unblinding of treatment assignment by the investigator is permitted and may be performed by the investigator through the IWRS system. This emergency unblinding may occur without prior authorization from the Sponsor. However, the investigator should promptly notify, document, and provide an explanation to the Sponsor for this premature unblinding.

If a JMC safety review is necessary, as outlined in the guidelines of the JMC Agreement, the JMC will instruct the IWRS to provide the treatment assignment for those patients of interest to evaluate unbalanced toxicity.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Ipatasertib (GDC-0068) and Placebo

Ipatasertib will be supplied by the Sponsor.

Ipatasertib drug product is intended for oral administration and will be supplied as 100 and 200 mg tablets. Ipatasertib and placebo tablets should be in the original high-density polyethylene bottles that includes the desiccant; do not store above 30°C (86°F); do not freeze. During dispensing of the tablet from the primary container, if the desiccant is removed, it should be placed back into the primary container until the last tablet is consumed. The period between dispensing and last tablet consumed should not exceed 1 month. The investigational product is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for patient use or returned to the Sponsor.

For information on the formulation, packaging, and handling of ipatasertib, see the pharmacy manual and the Ipatasertib Investigator's Brochure.

4.3.1.2 Paclitaxel

For information on the formulation, packaging, and handling of paclitaxel, see the local prescribing information for paclitaxel.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Ipatasertib (GDC-0068) and Placebo

Study treatment to either ipatasertib or placebo will be assigned by IWRS. Ipatasertib or placebo will be administered orally QD, beginning on Cycle 1, Day 1 through Day 21 of each 28-day cycle for a total of 3 cycles of treatment. Patients in the experimental arm will receive ipatasertib at a dose of 400 mg QD, and those in the control arm will receive placebo on the same days. Ipatasertib or placebo will be administered prior to the IV infusion of paclitaxel. Each dose of ipatasertib or placebo should be taken with a minimum of 3 ounces (90 mL) of fluid. Ipatasertib or placebo may be taken with or without food. If a dose is missed (not taken within 8 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.

The dose of ipatasertib or placebo will be taken at home, as directed on all days when there are no scheduled clinic visits. Ipatasertib or placebo should be taken at approximately the same time each day. On study visit days or visit days that require a blood draw for PK sampling, patients should not take their dose of ipatasertib or placebo at home before reporting to the clinic. Patients will be instructed to take their oral dose of ipatasertib or placebo at the clinic after completion of the pretreatment assessments outlined in Appendix 1.

A sufficient amount of ipatasertib or placebo should be provided to the patient to last for up to one treatment cycle (i.e., approximately 28 days). In some cases, extra tablets may be dispensed if there is a possibility that the patient's next visit may be delayed (e.g., due to holiday, inclement weather, or distance of patient's home from study center). Patients will also be given instructions for self-administration on dosing days that do not coincide with clinic visits.

Patients will be asked to record the time and date they take each dose in a medication diary. Patients will be instructed to bring their bottles of ipatasertib or placebo (including all unused tablets) and their medication diaries to each study visit for assessment of compliance and medication disposal.

The investigator (or designated representative) is responsible for keeping accurate records of the clinical supplies received from the Sponsor, including the amount dispensed to each patient and the amount returned by each patient. Study drug accountability (verification of the total number of tablets administered) for each patient should be performed as indicated in Appendix 1.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

Any dose modification, overdose, or incorrect administration of ipatasertib or placebo should be noted on the Study Drug Administration electronic Case Report Form (eCRF).

Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. Section 5.3.5.11 summarizes available safety data related to overdosing of ipatasertib.

4.3.2.2 Paclitaxel

The dose of paclitaxel in this study is 80 mg/m^2 administered by IV infusion on Days 1, 8, 15, and 22 of each 4-week cycle, for a total of 3 cycles of treatment *(12 total doses)*. Calculation of body surface area for the purposes of dosing of paclitaxel should be made according to the prescribing information. If the patient's weight changes by $>10\%$ during the study, the body surface area and drug doses should be recalculated, per institutional guidelines.

On the planned day of treatment, chemotherapy may be administered if:

- ANC $\geq 1500/\mu L$ (or per institutional guideline)
- Platelet count $\geq 100{,}000/\mu L$ (or per institutional guideline)
- Grade ≤ 2 clinically significant chemotherapy-related gastrointestinal toxicity

Because of the known potential for allergic reactions to paclitaxel and/or the Cremophor® vehicle, precautions must be taken to decrease the risk of anaphylaxis. Patients must be premedicated prior to paclitaxel per institutional practice with dexamethasone, diphenhydramine, and one of the following two H_2-receptor blockers: ranitidine or famotidine. Other H_2-receptor antagonists, such as cimetidine, which are known to inhibit cytochrome P450, are excluded. An H_1-receptor antagonist, such as diphenhydramine 50 mg IV, may be given as well.

The paclitaxel infusion will be delivered over at least 60 minutes for each dose per institutional guidelines and administered after the oral dose of ipatasertib or placebo.

Patients should be monitored during paclitaxel administration per institutional policies. Patients may receive anti-emetic and other prophylactic treatments (e.g., IV infusions of calcium and magnesium to try and decrease any potential peripheral neuropathy) according to institutional and/or local standards and per manufacturer's instructions.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5.

Any dose modification, overdose, or incorrect administration of paclitaxel should be noted on the Paclitaxel Administration eCRF. Adverse events associated with an overdose or incorrect administration of paclitaxel should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (ipatasertib/placebo) will be provided by the Sponsor where required by local health

authority regulations. The remaining IMP (paclitaxel) will either be provided by the Sponsor or sourced commercially by the site. The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Post-Trial Access to Ipatasertib

The Sponsor (Genentech) is a member of the Roche group and is subject to Roche's global policies. The Sponsor will offer post-trial access to the study drug (ipatasertib) 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 study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug 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 study drug after the end of the study if any of the following conditions are met:

- The study drug 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 study drug or data suggest that the study drug is not effective for TNBC
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for TNBC
- Provision of study drug 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 Web site:

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

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 28 days prior to screening to the end of the study visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who experience toxicities may be treated symptomatically as clinically indicated. Patients treated with anti-convulsant medications (see Section 4.4.2) should have levels monitored regularly.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study (within 7 days prior to Day 1 until end of study treatment) unless otherwise specified below or in the exclusion criteria in Section 4.1.2:

- Anti-cancer therapy: No additional investigational or commercial anti-cancer agents such as chemotherapy (with the exception of paclitaxel), immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy will be allowed.
- Radiation therapy: Radiation therapy should not be administered to the breast and/or regional lymph nodes prior to surgery in this study.
- Bone-targeted therapy: treatment including bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors are prohibited except for the management of osteoporosis in patients who have been receiving them at a stable dose for at least 2 weeks prior to randomization.
- Quinidine and/or other anti-arrhythmic agents, with the following exception:

  Stable doses of beta-blockers and/or calcium-channel blockers are permitted.
- Vaccination with a live vaccine should be avoided in patients receiving paclitaxel because of the potential for serious or fatal infections

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

A clinical study in patients shows that ipatasertib at a dose of 600 mg QD is a moderate inhibitor of CYP3A, which resulted in a 2.2-fold increase in midazolam exposures. Midazolam is a sensitive CYP3A substrate. Therefore, the following drugs should be used with caution. If use of one of these drugs is necessary, the risks and benefits

should be discussed with the Medical Monitor prior to its concomitant use with ipatasertib or placebo:

- Strong CYP3A4/5 inhibitors: Such as but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, and/or grapefruit juice or grapefruit supplements
- Strong CYP3A4/5 inducers: Such as but not limited to rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- CYP3A4 substrates with a narrow therapeutic index: Such as but not limited to alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine

The above lists of 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 is a strong CYP3A4/5 inhibitor or inducer or a CYP3A4 substrate with a narrow therapeutic index. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

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

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments performed during the study.

All patients will be closely monitored for safety throughout the study and during the adverse event reporting period (see Section 5.3.1). Study assessments will be performed at screening, during treatment, and at the treatment completion visits. Screening assessments will be performed within 28 days before first dose of study treatment, unless otherwise specified. A post-surgery assessment should be performed within 4 weeks of the patient's surgery.

4.5.1 Descriptions of Study Assessments

4.5.1.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

4.5.1.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer treatments, cancer procedures, and history of weight loss), disease characteristics (histologic subtype, stage of disease, and immunostaining or

in-situ hybridization results), and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, and nutritional supplements) used by the patient within 28 days prior to the ICF signature.

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

4.5.1.3 Physical Examinations

A complete physical examination should include the evaluation of head, eye, ear, nose, and throat; cardiovascular; dermatological; musculoskeletal; respiratory; gastrointestinal; and neurological systems, clinical breast examination and regional lymph node examination, as well as measurement of weight and height (height at screening only). Any abnormality identified at baseline should be recorded on the General Medical History and Vital Signs eCRF.

At subsequent visits (or as clinically indicated), targeted physical examination (including clinical breast examination and regional lymph node examination) should be performed to assess and record changes from baseline abnormalities and any treatment-emergent signs or symptoms. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. See Section 4.5.1.6 for the clinical breast examination requirements.

As part of tumor assessment, physical examinations should also include evaluation of the presence and degree of enlarged lymph nodes, as well as a breast examination.

ECOG performance status and weight will be recorded at baseline and throughout the study, as scheduled.

4.5.1.4 Vital Signs

Vital signs will include measurements of heart rate; systolic and diastolic blood pressure while the patient is in a seated position after resting for at least 5 minutes; respiratory rate; and oral, axillary, or tympanic temperature.

On paclitaxel dosing days, vital signs will be recorded prior to dosing and at the end of the infusion.

4.5.1.5 Distant Sites Tumor Assessment

Baseline distant sites tumor staging procedures should be performed at the discretion of the treating investigator. As a reference, per National Comprehensive Cancer Network (NCCN) guidelines, metastatic evaluation can be informed from clinical stage as follows:

- For Stage II and Stage IIIA: bone scan is to be performed in presence of bone pain and/or elevated alkaline phosphatase; abdominal/pelvic CT in case of elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms or abnormal physical examination; chest CT if pulmonary symptoms.

In addition, liver function tests, bone scans, chest X-rays/diagnostic CT, liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease.

4.5.1.6 Tumor and Response Evaluations

All measurable disease must be documented at screening and re-assessed at subsequent tumor evaluation (see Appendix 3). Response will be assessed by the investigator on the basis of clinical breast examinations and breast MRI. Whenever possible, assessments should be performed by the same evaluator to ensure internal consistency across visits.

Mammogram

Bilateral mammograms must be obtained at baseline within 90 days prior to enrollment, if not already performed per standard of care within this timeframe. Mammographic tumor measurements must be recorded in the eCRF.

Clinical Breast Examination

Assessment of primary breast tumor and regional lymph nodes must be done by physical examination (palpation) at baseline and as specified in Appendix 1. Breast tumor measurement by caliper (preferred) or ruler will be performed and recorded in the eCRF.

Axillary lymph node status (and other regional lymph nodes if clinically indicated) will also be assessed as clinically positive or negative at each timepoint. The main purpose of performing this examination is to rule out progressive disease that would lead to study treatment discontinuation.

Breast MRI

Contrast-enhanced breast MRI scans is mandatory for all patients at baseline (within 28 days prior to start of study treatment, Cycle 1 Day 1) and at the presurgical visit.

Timing and location of any clip or marker placement during study biopsies should be recorded for reference when MRI scans are read. If the screening breast MRI scan is not evaluable for RECIST measurement due to technical limitations of the scan itself, the scan may be repeated. Other MRI acquisition sequences, such as diffusion-weighted imaging, may be acquired during this study during the MRI scan visits for each patient.

If at any time there is suspicion of progression based on physical examination, then the algorithm provided in Figure 3 must be followed for further evaluation of the suspected progression.

For information about patient preparation, scanner requirements and settings, and image acquisition, refer to the imaging manual. Standard site practice may be followed for the use of mild sedatives or anti-anxiolytics for claustrophobic patients prior to MRI.

An independent radiologic review facility will be used for the purpose of collecting and assessing the quality of patient imaging scans throughout the trial. The review facility will retain copies of scans for potential centralized assessments of MRI-related endpoints.

4.5.1.7 Laboratory, Biomarker, and Other Biological Samples

Adequate hematologic and organ function within 14 days before the first study treatment must be determined. Predose laboratory samples should be drawn within approximately 3 days prior to study drug administration on Day 1 of each cycle, and results available before dosing. Postdose laboratory samples should be drawn according to the schedule in Appendix 1.

Local Laboratory Samples

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

- Hematology: Complete blood count, including red blood cell (RBC) count, ANC, hemoglobin, hematocrit, and white blood cell (WBC) count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count
- Coagulation: INR, PT, and aPTT/PTT
- Fasting (≥8-hour fast) serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN)/urea, creatinine, calcium, phosphorus, magnesium, total bilirubin, total protein, albumin, LDH, ALT, AST, and alkaline phosphatase.
- Fasting (≥8-hour fast) lipid profile and amylase: Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, amylase, and lipase
- Fasting insulin
- Glycosylated hemoglobin (HbA_{1c})
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Pregnancy test: All women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. Urine or serum pregnancy tests will be performed at specified subsequent visits, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Central Laboratory Samples

Instruction manuals outlining sampling procedures, storage conditions, and shipment instructions and supply kits will be provided for all central laboratory assessments. Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Mandatory tumor tissue: All biopsies collected for study purposes, whether it is required or optional, should be from safely accessible tissue and be minimally invasive
- Specimens will be used for assessment of several biomarkers. It is likely that not all assays will be performed on samples provided by each patient (possibly because of insufficient tumor material or inadequate sample quality). Therefore, assays will be performed with the following priority to ensure a high likelihood of generating data to support the objectives of the study, including but not limited to hematoxylin and eosin (H&E) stains, PTEN status by IHC, INPP4B status by IHC, RNA isolation for gene expression analysis, PIK3CA alteration analysis, AKT3 analysis, Ki67 staining, DNA isolation for additional mutation detection and copy number analyses, and RPPAs. In addition, other exploratory assessments, including but not limited to, AKT/PTEN signaling pathways may be evaluated, including protein expression and molecular profiling studies such as next-generation sequencing (NGS) and gene-expression.

    Archival tumor tissue for PTEN status: Tissue should be of good quality based on total and viable tumor content. Evaluation of the patient's tumor sample for PTEN status by a central laboratory must occur prior to initiation of study treatment. A minimum of 10 unstained slides from a prior diagnostic FFPE core biopsy would be required for enrollment eligibility purposes. Cytologic or FNA samples are not acceptable.

    If archival tissue is either insufficient or unavailable, FFPE core sample from a pretreatment biopsy of the tumor may be used; however, evaluation of the patient's tumor sample for PTEN status by a central laboratory should occur prior to the initiation of study treatment.

    Screening and on-treatment tumor tissue biopsy: FFPE and non-FFPE samples will be prepared from newly collected (fresh) tumor biopsies. At least one FFPE core needle biopsy and at least two freshly frozen OCT core needle biopsies are required at baseline and Cycle 1, Day 8.

    Tissue from surgery (see Section 3.1.1): A FFPE tumor block and/or representative tissue sample slides from the scheduled surgical resection are required for additional pathway marker evaluation.

        If a tumor block and/or slides cannot be obtained for various reasons (e.g., the tumor tissue is not sufficient at surgical resection), the site should discuss with the Sponsor.

    Mandatory tissue biopsy if patient will have additional systemic therapy prior to surgery: FFPE and non-FFPE samples will be prepared from newly collected (fresh) tumor biopsies. At least one FFPE core needle biopsy and at least two

freshly frozen OCT core needle biopsies are required prior to initiation of additional systemic therapy.

- Optional tumor tissue from biopsies at progression: Optional FFPE tumor biopsy collection is strongly recommended and may be obtained if the patient progresses during neoadjuvant treatment. Patients must have provided specific consent to allow collection and retention of optional samples.
- Plasma samples for exploratory research on candidate biomarkers including, but not limited, to ctDNA
- At Cycle 1, Day 1, a whole blood sample will be taken for DNA analysis and will be collected as part of the central laboratory samples.
- Plasma samples for PK assessment: Plasma samples will be collected to measure ipatasertib concentrations (see Appendix 1 and Appendix 2).
- Any remaining samples collected for PK and biomarker assays may be used for exploratory biomarker profiling, metabolite profiling and identification, and pharmacodynamic assay development purposes as appropriate.

  Residual samples will be destroyed no later than 5 years after the date of final closure of the clinical database.

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.5.

4.5.1.8 Electrocardiograms

Triplicate 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of assessments (see Appendix 1). Three interpretable ECG recordings (e.g., without artifacts) must be obtained at each timepoint (±5 minutes). The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Single ECG recordings may be obtained at unscheduled timepoints as indicated.

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.

If at a particular postdose timepoint the mean QTcF is > 500 ms and/or 60 ms longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and triplicate ECG monitoring should continue until QTcF has stabilized on

two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained and collected subsequent to the ECG reading. A decision on study drug discontinuation should be made, as described in Section 5.1.5.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.1.9 Pathology Assessment at Surgery

Determination of pathological complete response (pCR) will be as measured by local pathology laboratory evaluation of the breast and lymph node sampling from the axilla. Pathologic response within the breast and axilla will be assessed per local guidelines.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

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

Screening and pretreatment tests and evaluations will be performed within 28 days preceding Cycle 1, Day 1, unless otherwise specified. Results of tests and/or examinations performed as standard of care prior to obtaining informed consent and within 28 days prior to the first dose of study treatment may be used rather than repeating required tests. Additional informed consent (with a separate ICF) is required for collection of optional samples.

4.5.2.2 Assessments during Treatment

All visits must occur within 3 days (±3 days) of schedule visits after Cycle 1, Day 1, unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration of each cycle should be performed prior to study drug administration, unless otherwise noted.

The surgery visit should take place no more than 5 weeks after the last dose of paclitaxel.

4.5.2.3 Post-Surgery/Early Termination Assessments

A treatment completion visit should be scheduled within approximately 4 weeks after surgery. The treatment completion visit procedures and assessments should be performed after patients permanently discontinue all study treatments (i.e., ipatasertib or placebo, and paclitaxel).

Patients who receive additional neoadjuvant systemic treatment for significant residual disease or progressive disease will be followed for pathologic complete response after definitive surgery.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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 at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance (e.g., missed doses, visits)

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

Adverse events that are ongoing at the post-surgery/early termination visit and thought to be related to ipatasertib or placebo, and/or paclitaxel, will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable for a minimum of 60 days, new anti-tumor treatment is initiated, the patient is lost to follow up, the patient withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse event.

4.6.2 Study Treatment Discontinuation

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

- Pregnancy
- Disease progression, per investigator assessment
- Intolerable toxicity to ipatasertib or placebo, and/or paclitaxel
- Change in patient eligibility

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site 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.

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ipatasertib is not approved and is currently in clinical development. Thus, the entire safety profile is not known at this time. The following information is based on nonclinical data and limited clinical data from the Phase I studies.

Nonclinical and Phase I clinical data for ipatasertib as a single agent and in combination with chemotherapy have identified limited overlap with the well-defined safety profile of paclitaxel. The combination of ipatasertib and paclitaxel has been well tolerated in the Phase Ib study (PAM4983g), including ipatasertib administered at the RP2D of 400 mg in combination with paclitaxel. However, given that both ipatasertib and paclitaxel may result in gastrointestinal toxicity, there may be an increased risk of nausea, vomiting, and diarrhea with this combination. The potential for a clinically meaningful change in the exposure of ipatasertib and/or paclitaxel because of drug–drug interaction (DDI) is anticipated to be low, based on the PK data from the Phase Ib study (PAM4983g).

The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

5.1.1 Eligibility Criteria

Eligibility criteria for this study (see Section 4.1) were selected to enhance the safety of patients in this trial. A number of exclusion criteria are specifically based on the known

safety profiles of the study treatments, including the known safety profile of paclitaxel, as well as the nonclinical and clinical data for ipatasertib.

5.1.2 Safety Monitoring

Safety will be evaluated in this current study through the monitoring of all serious adverse events, non-serious adverse events, and laboratory abnormalities, defined and graded according to NCI CTCAE, v4.0. *In addition, the JMC will conduct analyses of safety (see Section 6.8.1 and Section 6.8.2*).

5.1.3 Risks Associated with Ipatasertib

As of 31 March 2014, single-agent ipatasertib had been given to 30 patients with cancer in the dose-escalation stage. The following adverse events have been assessed as related to ipatasertib and occurred in ≥ 10% of the patients: nausea, diarrhea, vomiting, asthenia, hyperglycemia, decreased appetite, dyspepsia, dysgeusia, and rash. Grade 3 adverse events that were assessed as related to ipatasertib were diarrhea, asthenia, hypercholesterolemia, hyperglycemia, hypophosphatemia, nausea, and toxic skin eruption (see Section 1.2.2 and Ipatasertib Investigator's Brochure for more details).

The combination of ipatasertib with paclitaxel has also been tested in Arm C of the ongoing Phase Ib study (PAM4983g). The types and frequencies of adverse events assessed by investigators to be related to ipatasertib in Study PAM4983g are comparable to the single-agent Study PAM4743g. The following adverse events in Arm C (ipatasertib in combination with paclitaxel) have been assessed as related to ipatasertib in combination with paclitaxel and occurred in ≥ 10% of the patients: diarrhea, nausea, fatigue, vomiting, rash, abdominal pain, anemia, dehydration, dermatitis acneiform, dizziness, dyspnea, and hyperglycemia. Grade 3 adverse events assessed as related to ipatasertib in Arm C were diarrhea, dehydration, hyperglycemia, anemia, neutropenia, and rash. Of note, no patients in Arm C experienced a Grade 4 or Grade 5 adverse event assessed as related to ipatasertib. A more comprehensive list of adverse events observed in Study PAM4983g is provided in Section 1.2.2.

Refer to the Ipatasertib Investigator's Brochure for further information regarding the nonclinical and clinical safety evaluation of ipatasertib as a single-agent and in combination with chemotherapy.

5.1.4 Potential Safety Issues Associated with Paclitaxel

In prior clinical trials of paclitaxel, the following safety signals associated with paclitaxel were identified: nausea, vomiting, diarrhea, stomatitis, peripheral neuropathy, hypersensitivity reactions, and hematologic toxicity.

To be eligible for the current study, patients must have adequate hematologic function, as manifested by measurements of complete blood cell counts. Furthermore, blood cells will be assessed prior to each treatment cycle (every 4 weeks) or sooner if clinically indicated.

Peripheral neuropathy has not been observed to date with single-agent ipatasertib in the Phase Ia study (PAM4743g). Patients with Grade ≥2 peripheral neuropathy will be excluded from this study. Patients will be monitored throughout the study for new peripheral neuropathy through assessment of adverse events and physical examinations. Modifications of paclitaxel administration in response to neuropathy are described below.

Patients will be monitored for other paclitaxel-associated adverse events as outlined in this section. For more details regarding the safety profile of paclitaxel, see the Paclitaxel Package Insert or Summary of Product Characteristics

5.1.5 Dosage Modifications

Guidelines for dosage modification and treatment interruption or discontinuation are provided below.

5.1.5.1 General Guidelines

Dose modifications for paclitaxel chemotherapy will be performed according to standard practice or institutional guidelines; details in this section can be used as guidance. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

General guidelines for dosage/schedule modification are summarized as follows:

- All effort should be made to provide 12 total doses of paclitaxel, if risk/benefit assessment allows.
- If ipatasertib or placebo treatment is delayed, paclitaxel treatment should continue *as scheduled; however, if paclitaxel treatment is delayed and ipatasertib/placebo is scheduled to be administered at the same timepoint, it is preferred that ipatasertib/placebo is also delayed to align with paclitaxel dosing*.
- If toxicity causes paclitaxel treatment to be delayed, clinic visits (and study procedures) associated with each cycle of therapy, as defined by the administration of paclitaxel chemotherapy, will also be delayed. However, laboratory assessments and clinical visits shall be scheduled as needed for adverse events follow-up. Once the toxicity has resolved to the required level, study treatment and study procedures will be resumed, according to the study cycle day count.
- For any concomitant conditions at baseline, the dose modifications will apply according to the shift in toxicity grade, if the investigator deems it appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and will be treated as Grade 1 toxicity for dose-modification purposes.
- For toxicities assessed by the investigator to be unlikely to develop into serious events, treatment may be continued at the same dose without reduction or interruption. Dose reductions or interruptions may not be required for anemia (non-hemolytic) if satisfactorily managed by transfusions.

- If any observed toxicity is attributable to only one drug as assessed by the investigator, the dose of the other drug(s) may not require modification.
- Dose modifications for isolated abnormal hematologic laboratory values will be based on hematologic parameters at the start of a treatment cycle.
- Patients who require chemotherapy dose reductions and tolerate the reduced dose for across three or more doses (i.e., at least 21 days) may be allowed to increase back to a 100% dose at the treating physician's discretion.
- Chemotherapy may be delayed to manage toxicity. Delays up to 4 weeks (approximately 28 days) are permitted. Any delay longer than 4 weeks for a treatment-related adverse event will require permanent discontinuation of paclitaxel. All effort should be made to provide 12 total doses of paclitaxel, if risk/benefit allows.

Criteria for treatment modifications and guidelines for the management of toxicities attributable to ipatasertib, placebo, and/or paclitaxel are summarized below, along with recommended dose reductions for ipatasertib, placebo, and/or paclitaxel (see Table 1). The suggested reduction instructions provided in Table 1 are intended to serve as a guideline to allow ongoing treatment for patients.

Table 1 Suggested Dose Reductions for Ipatasertib, Placebo, and/or Paclitaxel

Dose Level [a]	Ipatasertib/Placebo	Paclitaxel
Starting dose	400 mg	80 mg/m^2
First dose reduction[b]	300 mg	65 mg/m^2
Second dose reduction[b]	200 mg	50 mg/m^2
Third dose reduction[b]	Discontinue	Discontinue

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

[b] *Note that dose modification(s) for ipatasertib/placebo and paclitaxel are independent (e.g., adverse event may lead to dose reduction for ipatasertib/placebo with no dose modification for paclitaxel).*

5.1.5.2 Dosage Modification for Ipatasertib and Placebo

Patients may hold the ipatasertib or placebo for up to 4 consecutive weeks (approximately 28 consecutive days) in order to recover from toxicity or an adverse event related to the study drug. If the ipatasertib or placebo is discontinued at any time during the study, patients may have the option of continuing on study with chemotherapy alone.

If the patient does not tolerate the QD dosing of the ipatasertib or placebo, a BID regimen of the ipatasertib or placebo (with the total daily dose divided in half, without a dose reduction, and administered approximately every 12 hours) may be attempted (e.g., a 400 mg QD dose may be divided into 200 mg administered BID). The BID

regimen may be used to alleviate gastrointestinal symptoms, including nausea *and* vomiting. Employment of a BID regimen should not be considered as a dose reduction. No more than two dose reductions of ipatasertib or placebo per patient (lowest dose level to be administered will be 200 mg/day) will be allowed, and dose re-escalation of ipatasertib or placebo may be permitted in the study after discussion with the Medical Monitor.

5.1.5.3 Fasting Hyperglycemia

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 4 hours. Dosage modification guidelines for fasting hyperglycemia attributable to ipatasertib or placebo are outlined below:

- Grade 1 fasting hyperglycemia (Range: >ULN–160 mg/dL [>ULN–8.9 mmol/L]): The patient may continue treatment with the ipatasertib or placebo, and chemotherapy. The patient may receive education on a diabetic diet and consider beginning home glucose monitoring at the discretion of the investigator. If glucose home monitoring is instituted, the ipatasertib or placebo treatment decision should be based on the morning fasting glucose value obtained prior to the dose of ipatasertib or placebo. The patient may be started on an oral anti-diabetic medication (e.g., metformin) at the discretion of the investigator.
- Grade 2 fasting hyperglycemia (Range: >160–250 mg/dL [>8.9–13.9 mmol/L]): The patient should be started on an oral anti-diabetic medication (e.g., metformin) and should receive education on a diabetic diet. The ipatasertib or placebo treatment decision should be based on the morning fasting glucose value obtained prior to the dose of ipatasertib or placebo. The patient may also continue treatment with the ipatasertib or placebo, and/or chemotherapy.
- Grade ≥3 fasting hyperglycemia (Range: >250–500 mg/dL [>13.9–27.8 mmol/L]): The ipatasertib or placebo should be held until fasting hyperglycemia has resolved to Grade ≤2, but may continue chemotherapy. The patient should start a diabetic diet and should start an oral anti-diabetic medication (e.g., metformin). The patient may begin home glucose monitoring (with fasting glucose checked prior to the ipatasertib daily dose). If fasting glucose levels recover to Grade ≤2 within 3 days, the ipatasertib or placebo may be resumed at the same dose; alternatively, the dose of ipatasertib or placebo may be reduced by one dose level (see Table 1) at the discretion of the investigator. If Grade≥3 fasting hyperglycemia recurs within the same cycle, or if recovery of fasting glucose levels to Grade ≤2 takes 4 or more days, the dose of ipatasertib or placebo must be reduced by one dose level when treatment resumes.

If patients develop Grade ≥3 fasting hyperglycemia associated with severe neurological symptoms (e.g., lethargy, focal signs, and obtundation), hyperventilation, abdominal pain or hypotension, discontinuation of study treatment with ipatasertib or placebo should be considered and discussed with the Medical Monitor. Patients should be educated on the symptoms of hyperglycemia so that they can be promptly and appropriately managed.

In order to diminish the risk of hypoglycemia, insulin should not be administered for asymptomatic hyperglycemia of any grade.

5.1.5.4 Neutropenia and/or Thrombocytopenia

Addition of hematopoietic growth factors is allowed. Dosage modification guidelines for neutropenia and/or thrombocytopenia attributable to paclitaxel are outlined below:

- Grade 2 neutropenia or thrombocytopenia: Paclitaxel may be administered at the previous dose when ANC has recovered to ≥1500/μL (or per institutional guideline) and when the platelet count has recovered to ≥100,000/μL (or per institutional guideline). If the hematologic parameters do not recover to levels required for dosing per guidelines within 14 days, the paclitaxel dose should be reduced.
- Grade ≥3 neutropenia or thrombocytopenia: Paclitaxel should be held. Dose for subsequent paclitaxel treatments should be reduced by one dose level (see Table 1). Following a treatment delay of 4 weeks, if recovery to ANC of ≥1500/μL (or per institutional guideline) or if recovery to platelet count of ≥100,000/μL (or per institutional guideline) does not occur before the next scheduled paclitaxel dose, the patient will permanently discontinue paclitaxel treatment.
- Febrile neutropenia (ANC <1000/μL and fever ≥38.5°C [101°F]): Paclitaxel should be held until adequate recovery and for up to 4 weeks. If the neutropenia recovers to ANC ≥1500/μL within 4 weeks, paclitaxel should be reduced by one level. Following a treatment delay of up to 4 weeks, if recovery to ANC of ≥1500/μL does not occur, the patient will permanently discontinue paclitaxel treatment.

If a dose delay is required as a result of neutropenia at any grade, patients should receive prophylactic granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) per institutional standards.

Patients should be counseled as to the risk of fever and infection and to the importance of contacting their treating physician immediately if these conditions occur, so that they can be promptly and appropriately managed.

5.1.5.5 Nausea and/or Vomiting

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron (or equivalent anti-emetic). If the nausea and/or vomiting are attributable to the ipatasertib or placebo, the investigator may employ a BID dosing of the ipatasertib or placebo administration (equivalent to the total daily dose divided by half; see Section 5.1.5.2). For persistent nausea and/or vomiting attributable to the ipatasertib or placebo, and/or paclitaxel, dosage modification guidelines for ipatasertib or placebo, and/or paclitaxel are outlined below:

- Grade 1 nausea and/or vomiting: Maximum supportive care should be administered as needed at the discretion of the investigator.
- Grade 2 nausea and/or vomiting: Ondansetron (or equivalent anti-emetic) should be administered as needed.

- Grade ≥3 nausea and/or vomiting: Ondansetron (or equivalent anti-emetic) should be administered as needed. If the nausea and/or vomiting are attributable to ipatasertib or placebo, the investigator may employ a BID dosing of ipatasertib/placebo administration (equivalent to the total daily dose divided by half; see Section 5.1.5.2); alternatively, the dose of ipatasertib or placebo may be reduced by one dose level (see Table 1). If nausea and/or vomiting is attributable to chemotherapy, paclitaxel may be given at a reduced dose during subsequent cycles.

Dose re-escalation of the ipatasertib or placebo, and/or paclitaxel may be permitted in subsequent cycles for patients who exhibit Grade ≤1 nausea/vomiting through at least one cycle.

5.1.5.6 Diarrhea

Diarrhea should be managed with loperamide or per *local guidelines and standard of care, including but not limited to therapy with Lomotil (diphenoxylate and atropine), codeine, or octreotide.* Dose reductions for diarrhea should occur only if the symptoms persist despite treatment with adequate (combination) anti-diarrheal medications.
If persistent diarrhea *(more than 48 hours despite optimal medical treatment or dose hold)* is attributable to the ipatasertib or placebo, and/or paclitaxel, dosage modification guidelines for ipatasertib or placebo, and/or paclitaxel are outlined below:

- Grade 2 diarrhea: The investigator *should initiate optimal medical management with loperamide as early as possible. If diarrhea is persistent (lasting longer than 48 hours despite medical management), second-line therapy* may *include (but not limited to) Lomotil (diphenoxylate and atropine), codeine or octreotide per local guidelines and standard* of *care. Ipatasertib/placebo dosing should be interrupted until improvement of diarrhea to Grade ≤ 1, at which time* ipatasertib*/placebo may be resumed at* the *same* dose *for initial occurrence with consideration of maintenance loperamide dosing (i.e., 2 mg, 2 to 4 times daily). Investigators may* reduce ipatasertib or placebo by one dose level (see Table 1) *for recurrent Grade 2 diarrhea*. If diarrhea persists following *up to two* dose reduction*s* of ipatasertib or placebo, consider dose hold of paclitaxel*. Dose intensity of paclitaxel should be maintained as much as is safely possible. Paclitaxel* dose *reduction or discontinuation can be considered if diarrhea persists even after ipatasertib/placebo discontinuation* (see Table 1).
- Grade ≥3 diarrhea: Medical management of diarrhea per Grade 2 diarrhea above should be initiated as early as possible. Ipatasertib or placebo should be held until the diarrhea resolves to Grade ≤1, at which time maintenance loperamide dosing (i.e., 2 mg, 2 to 4 times daily) is recommended. The dose of ipatasertib or placebo will be reduced by one dose level when treatment resumes (see Table 1). If diarrhea persists following dose reduction of ipatasertib or placebo, an additional dose hold or reduction with ipatasertib/placebo should be considered (see Table 1). Dose intensity of paclitaxel should be maintained as much as is safely possible. Paclitaxel dose reduction or discontinuation can be considered if diarrhea persists even after ipatasertib/placebo discontinuation *(see Table 1)*.

Dose re-escalation of the ipatasertib or placebo, and/or paclitaxel may be permitted in subsequent cycles for patients who exhibit Grade ≤1 diarrhea for at least one cycle *after discussion with the Medical Monitor*.

Gastroenterologists should be counseled as to the risk of colitis and infection upon prolonged diarrhea condition, and patients should be educated on the symptoms of dehydration, so that patients can be promptly and appropriately managed.

For additional information on the management guideline for diarrhea, see Appendix 6.

5.1.5.7 Mucositis

Dosage modification guidelines for mucositis attributable to the ipatasertib or placebo, and/or paclitaxel are outlined below:

- Grade 1 or Grade 2 mucositis: Maximum supportive care should be administered as needed at the discretion of the investigator. If Grade ≥2 mucositis recurs in subsequent 4-week cycles, despite maximal supportive care, the dose of ipatasertib or placebo should be reduced by one dose level, and/or the dose of paclitaxel may be reduced for subsequent 4-week cycles (see Table 1).
- Grade ≥3 mucositis: If the mucositis resolves to Grade ≤2 during the current cycle, the dose of ipatasertib or placebo should be reduced by one dose level, and/or the dose of paclitaxel may be reduced by one dose level for subsequent cycles (see Table 1). If the mucositis does not resolve to Grade ≤2 during the current cycle, paclitaxel should be held for a maximum of 4 weeks (approximately 28 days). If the mucositis resolves to Grade ≤2 within a maximum of 4 weeks, dosing of paclitaxel may resume at dose reduced by one level for subsequent cycles (see Table 1). If recovery of mucositis to Grade ≤2 does not occur within a maximum of 4 weeks, the patient will permanently discontinue paclitaxel and may continue the ipatasertib or placebo after discussion with the Medical Monitor.

Dose re-escalation of the ipatasertib or placebo, and/or paclitaxel may be permitted in subsequent cycles for patients who exhibit Grade ≤1 mucositis for at least one cycle.

5.1.5.8 Skin Toxicity

Dosage modification guidelines for skin toxicity attributable to the ipatasertib or placebo, and/or paclitaxel are outlined below:

- Grade 1 or Grade 2 skin toxicity, asymptomatic: Investigator may prescribe topical or oral steroids or per institutional guidelines.
- Grade 2 skin toxicity, symptomatic: Investigator should consider topical or oral steroids per institutional guidelines. The ipatasertib or placebo, and/or paclitaxel treatment may be held until resolution to Grade ≤1 or resolution such that the skin toxicity is no longer clinically significant.

- Grade ≥3 skin toxicity attributable to ipatasertib or placebo: The ipatasertib or placebo should be held for a maximum of 4 weeks (approximately 28 days). During this time, the patient may continue treatment with paclitaxel at the discretion of the investigator. If the skin toxicity resolves to Grade ≤2 or resolution such that the skin toxicity is no longer clinically significant in less than 4 weeks, dosing of the ipatasertib or placebo may resume, but the dose of ipatasertib or placebo should be reduced by one dose level (see Table 1). If recovery of the skin toxicity to Grade ≤2 or resolution such that the skin toxicity is no longer clinically significant does not occur within a maximum of 4 weeks, the patient will permanently discontinue the ipatasertib or placebo but may continue paclitaxel.
- Grade ≥3 skin toxicity attributable to paclitaxel: Paclitaxel treatment should be held for a maximum of 4 weeks (approximately 28 days). If the skin toxicity resolves to Grade ≤2 within a maximum of 4 weeks, paclitaxel treatment may resume with paclitaxel dose reduced by one dose level (see Table 1). If recovery of the skin toxicity to Grade ≤2 does not occur within a maximum of 4 weeks, the patient will permanently discontinue paclitaxel but may continue the ipatasertib or placebo.

Dose re-escalation of the ipatasertib or placebo, and/or paclitaxel may be permitted in subsequent cycles for patients who exhibit Grade ≤1 skin toxicity for at least one cycle.

The ipatasertib or placebo, and/or paclitaxel should be permanently discontinued for rash due to Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction that is related to ipatasertib or placebo, and/or paclitaxel.

5.1.5.9 Peripheral Neuropathy

If Grade ≥3 peripheral neuropathy attributable to paclitaxel develops in patients, paclitaxel should be held until the neuropathy recovers to Grade ≤2 or resolution such that the peripheral neuropathy is no longer clinically significant. During this time, the patient may continue the ipatasertib or placebo at the discretion of the investigator. If the peripheral neuropathy recovers to Grade ≤2 within 4 weeks or resolution such that the peripheral neuropathy is no longer clinically significant, dosing of paclitaxel may resume reduced by one dose level (see Table 1). If recovery of the peripheral neuropathy to Grade ≤2 or resolution such that the peripheral neuropathy is no longer clinically significant does not occur within a maximum of 4 weeks, the patient will permanently discontinue paclitaxel but may continue the ipatasertib or placebo. Dose of paclitaxel may be reduced at discretion of the investigator for clinically significant neuropathy not reaching grade 3.

5.1.5.10 Hypersensitivity

If a hypersensitivity reaction due to infusion of paclitaxel develops in patients, treatment for the hypersensitivity reaction, including the possibility of rechallenge with paclitaxel, should be administered as per institutional guidelines or at the discretion of the investigator. The patient may continue the other study treatment components not associated with the toxicity (i.e., ipatasertib or placebo).

5.1.5.11 Other Non-Hematologic Toxicities

If other Grade ≥3 non-hematologic toxicities not described above develop in patients, treatment with the ipatasertib or placebo, and/or paclitaxel may be held, depending on the attribution of the toxicity, at the discretion of the investigator. During this time, treatment may continue with the other non-attributable treatment agent (i.e., either the ipatasertib or placebo, or paclitaxel). The Grade ≥3 non-hematologic toxicity should be monitored at least weekly. If the toxicity resolves to Grade ≤1 within 2 weeks, treatment may resume with the attributable agent. If the toxicity resolves to Grade ≤1 in 2–4 weeks, the dose of the attributable drug should be reduced by one level per the suggested guidelines in Table 1. Depending on the nature and the severity of the adverse event, if recovery to Grade ≤1 takes >4 weeks, treatment may resume with the attributable agent with dose reduction, or the attributable agent may be permanently discontinued, at the discretion of the investigator and after discussion with the Medical Monitor.

For Grade ≥3 toxicities associated primarily with laboratory abnormalities only (e.g., elevation of ALT, AST, lipase, or amylase, or decreases in phosphorus without clinical or other evidence of pancreatitis or other hepatic dysfunction), study treatment may continue without interruption and/or dose-reduction at the discretion of the investigator per institutional practice.

5.1.6 Management of Specific Adverse Events

Guidelines for the management of specific adverse events are provided below.

5.1.6.1 Hyperglycemia

Concomitant administration of the ipatasertib with food increased plasma glucose and insulin levels in the single-agent Phase Ia study (PAM4743g). Grade 1 or Grade 2 fasting hyperglycemia events were observed among fasting patients and were relieved with a combination of oral anti-diabetic therapy (e.g., metformin) and diet modifications. Patients who at baseline show early signs of insulin resistance, based on an elevated homeostasis model of estimated insulin resistance, may be treated with an oral anti-diabetic drug (e.g., metformin) and will still be allowed to participate in the trial. To prevent the risk of hypoglycemia, management of any asymptomatic hyperglycemia with insulin should be avoided.

Use of glucocorticoid pretreatment for paclitaxel may influence glucose metabolism in patients in this study. Institutions may use glucocorticoid premedications per institutional policies and as described in the package insert.

Patients who currently require the use of insulin or have a fasting glucose >150 mg/dL or HbA_{1C} >8% at baseline will be excluded from this study. Fasting glucose levels and HbA_{1C} will be obtained at selected study visits from all patients as described in Appendix 1. For the purposes of dose modification decisions, glucose measurements

should be in a fasting state, defined as a glucose level obtained ≥4 hours after the most recent caloric intake.

Any patient experiencing fasting hyperglycemia should be managed per standard medical practice for hyperglycemia and sequelae, such as dehydration and acidosis. Suggested dose modifications of the ipatasertib or placebo for hyperglycemia are outlined in Section 5.1.5.3.

Other metabolic effects observed with the class of PI3K/mTOR inhibitors include hypercholesterolemia and hypertriglyceridemia; therefore, patients with Grade ≥2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia will be excluded from the study. Fasting plasma lipid profiles will be obtained at selected study visits from all patients as described in Appendix 1.

5.1.6.2 Hematologic Toxicity

Lymphocyte depletion has been observed in nonclinical toxicity studies in animals treated with ipatasertib; therefore, patients will be required to have adequate hematologic function, with resolution of any acute hematologic toxicities from prior therapies, before initiation of ipatasertib or placebo. Patients with conditions that affect lymphocyte counts, such as HIV infection or immunosuppressive therapy, will be excluded from the study. Patients will have standard hematologic parameters monitored throughout the study as described in Appendix 1.

5.1.6.3 Gastrointestinal Toxicity

Nausea, vomiting, and diarrhea have been observed in the Phase Ia study (PAM4743g) with single-agent ipatasertib. These symptoms are generally transient and relieved by supportive medications (e.g., ondansetron for nausea and loperamide for diarrhea). Class effects from other PI3K/Akt pathway inhibitors have included stomatitis and diarrhea and are generally reversible.

Any potential gastrointestinal effects will be monitored by weekly evaluations of clinical history and physical examination findings. Patients with known active inflammatory diseases, including those with small or large intestinal inflammation (e.g., Crohn's disease or ulcerative colitis), will be excluded from the study.

Gastrointestinal toxicities should be managed according to institutional guidelines, with appropriate supportive care as clinically indicated. Suggested dose modifications of ipatasertib or placebo, and/or paclitaxel for gastrointestinal toxicities are outlined in Section 5.1.5.5 for nausea/vomiting, Section 5.1.5.6 for diarrhea, and Section 5.1.5.7 for mucositis.

5.1.6.4 Dermatologic Toxicity

Treatment-related rash occurred in approximately 12% of patients who received ipatasertib in the Phase Ia study (PAM4743g). This rash commonly manifested itself as

a maculopapular-type rash, with or without pruritus. The majority of cases were mild in severity and self-limited. The incidence and severity of the rash appeared to be dose-dependent and may occur during or upon stopping ipatasertib administration. Isolated cases of Grade 3 rash have been observed.

Rash and other dermatologic events should be closely monitored and managed according to institutional guidelines, with appropriate supportive care as clinically indicated. For severe rash, dosing of ipatasertib or placebo should be interrupted, and patients should be treated with supportive therapy according to standard-of-care practice. Suggested dose modifications of ipatasertib or placebo, and/or paclitaxel for dermatologic toxicity are outlined in Section 5.1.5.8.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious 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), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; 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 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious 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 include the following:

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is

considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Grade 4 fasting hyperglycemia or symptomatic Grade 3 fasting hyperglycemia
- Grade ≥4 hepatotoxicity
- Grade ≥3 colitis *or diarrhea*
- *Grade 2 diarrhea that persists for longer than 5 days despite optimal medical management (per diarrhea management in Section 5.1.5.6)*
- Grade ≥3 rash
- Grade ≥2 pneumonitis
- Any grade acute coronary syndrome or myocardial infarction

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, 5.5, and 5.6.

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug, or initiation of another anti-cancer therapy, whichever occurs first. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse events with a suspected causal relationship (see 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 (v4.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or

"no" accordingly. The following guidance should be taken into consideration (see also Table 3):

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

Table 3 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs

and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe 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*, unless the* severity *increases.* If a persistent adverse event becomes more severe, *it* should be recorded *as a separate event* on the Adverse Event eCRF. *The initial (less severe) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became more severe.* If *a persistent adverse* event becomes serious, it should be *recorded as a separate event on the Adverse Event eCRF and* 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 *initial (*non-serious*) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became* serious.

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ 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 if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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

5.3.5.5 Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

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

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

5.3.5.7 Deaths

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

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. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive

and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

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

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. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., 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.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- 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
- Perform an efficacy measurement for the study
- Receive scheduled therapy for the target disease of the study

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

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

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

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
- Non-serious adverse events of special interest
- Pregnancies

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted] *M.D.*

Telephone Nos.: [redacted] *(office)*

[redacted] *(mobile)*

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious 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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche 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 non-serious adverse events of special interest will be reported until 30 days after the last dose of study drug or 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 electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event / Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche 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 post-study adverse events 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 to immediately inform the investigator if they become pregnant during the study or within 30 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to Roche 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. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Congenital Anomalies/Birth Defects and Abortions

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, 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 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period and that is believed to be related to prior study drug treatment. The adverse event reporting period is defined as 30 days after the last dose of study drug or initiation of another anti-cancer therapy, whichever occurs first (see Section 5.3.1).

The investigator should report these events directly to Roche or its designee, either by faxing or by scanning and emailing the Serious Adverse Event / Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Ipatasertib Investigator's Brochure
- Local prescribing information for paclitaxel

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

Primary and secondary efficacy analyses will be based on randomized patients, with patients allocated to the treatment arm to which they were randomized.

Safety analyses will include treated patients (i.e., patients who received at least one dose of ipatasertib, placebo, or paclitaxel), with patients allocated to the treatment arm associated with the regimen that they actually received.

No adjustments will be made for multiple comparisons when addressing primary and secondary efficacy endpoints. Multiple comparison adjustments will be used for selected exploratory endpoints to account for genome-wide correlative comparisons.

The primary analysis will be performed after LPLV and subsequent data cleaning, expected to occur approximately 7 months after the last patient has been randomized to the study.

The primary, secondary, and exploratory efficacy analyses and safety analyses are described in Sections 6.4, 6.5, and 6.7.

6.1 DETERMINATION OF SAMPLE SIZE

This study is designed to evaluate the safety and preliminary evidence of activity of ipatasertib and paclitaxel. This trial is hypothesis-generating and is able to detect only a large benefit from combination therapy with ipatasertib and paclitaxel versus placebo and paclitaxel.

A total of 150 patients will be enrolled in the study (75 per arm). Assuming a 60% prevalence of PTEN-low status in TNBC, it is expected that 90 patients with PTEN-low tumors will be enrolled. This trial will not have adequate power to detect minimum clinically meaningful differences between treatment arms at a statistically significant α (type 1) error level of 5%. Instead, the 90% confidence intervals (CIs) for the difference in pCR rate will be calculated with the expectation that for clinically meaningful outcomes, the lower limit of the two-sided 90% CI will be greater than 0.

For example, a true improvement of greater than 20% in pCR rate (from 20% to 40%) would be considered a clinically meaningful outcome when comparing ipatasertib and paclitaxel versus placebo and paclitaxel. Given at least 90 patients (45 per arm) with PTEN-low tumors and a targeted improvement of 20% in pCR rate, the corresponding lower limit of the two-sided 90% CI is 2.3%. Also, for 150 patients (75 per arm) in ITT population with a targeted improvement of 15% in pCR rate, the corresponding lower limit of the two-sided 90% CI is 1.5%.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration, and discontinuation from the study will be summarized overall and by treatment arm. The reasons for study treatment discontinuation will be tabulated, and major protocol violations will be summarized.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race/ethnicity, region, weight, baseline ECOG performance status, tumor PTEN status, and tumor PIK3CA status will be summarized by treatment arm.

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

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the rate of locally assessed pCR in breast and axilla (ypT0/Tis ypN0). The primary efficacy analyses will be performed on randomized patients, with the patients allocated to the treatment arm according to the randomization. The pCR endpoint will be analyzed for all randomized patients and for patients with PTEN-low tumors. Patients whose pCR assessment is missing are counted as not achieving a pCR.

An estimate of the pCR rate and its 90% CI (Blyth-Still-Casella method) will be calculated for each treatment arm for all randomized patients and for patients with PTEN-low tumors. The difference in pCR rates will also be provided with 90% CIs, using the normal approximation to the binomial distribution. Stratified Cochran-Mantel-Haenszel tests will be used to compare treatment arms.

In addition, a sensitivity analysis may be conducted to account for patients whose pCR assessment cannot be ascertained.

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows.

- The rate of pCR in breast in all patients and in patients with PTEN-low tumors assessed by local evaluation
- Tumor ORR assessed by breast MRI via modified RECIST criteria, in all patients and in patients with PTEN-low tumors
- The rate of pCR and ORR in patients whose tumors are Akt Dx+ (defined by PTEN status, INPP4B status, and PI3K alterations)

- The rate of pCR according to subtypes of breast cancer defined by molecular profiles; e.g., PAM50 classifier
- The rate of BCS and conversion to BCS in patients with T2 or T3 tumors

These endpoint measures will be summarized by their point estimates and 90% CIs for each treatment arm, and will be compared between the two treatment arms for each population using the normal approximation to the binomial distribution. In addition, the locally-assessed pCR rate in breast and axilla will also be compared between the two treatment arms based on Cochran-Mantel-Haenszel test.

6.5 SAFETY ANALYSES

The safety analyses will include all treated patients (i.e., randomized patients who received at least one dose of ipatasertib, placebo, or paclitaxel), with patients grouped according to the treatment actually received.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, and ipatasertib or placebo, and paclitaxel exposures. Treated patients will be included in the safety analyses.

Verbatim descriptions of adverse events will be mapped to thesaurus terms. Treatment-emergent events (defined as events occurring on or after the first dose of ipatasertib, placebo, or paclitaxel) will be summarized by thesaurus term, appropriate thesaurus levels, and NCI CTCAE, v4.0 grade. Serious adverse events, including deaths, will be listed separately and will be summarized.

Relevant laboratory values will be displayed by time, with NCI CTCAE Grade 3 and Grade 4 values identified, where appropriate. Laboratory abnormalities will also be summarized by NCI CTCAE grade. Vital signs will be summarized by each treatment arm.

6.6 PHARMACOKINETIC ANALYSES

GDC-0068 levels will be measured on Day 1 and Day 8 of Cycle 1. GDC-0068 plasma concentration versus time data, together with information on dosing and patient characteristics, will be pooled and analyzed using a PopPK analysis approach, as appropriate. Nonlinear mixed-effect modeling will be used for the estimation of PopPK parameters for GDC-0068. 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/pharmacodynamic analyses may be reported in separate stand-alone reports. Additional analyses may be explored as warranted by the data.

6.7 EXPLORATORY ANALYSES

The exploratory endpoints, including the effects of PI3K/Akt pathway alterations in the archival tumor samples will be evaluated with appropriate methods.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Analyses

The JMC will convene for a review of partially unblinded summaries of the safety data after approximately 20 patients have completed study treatment, including surgery. In addition, after approximately 90 patients have completed study treatment as well as surgery, the JMC will reconvene to perform an interim safety and efficacy analysis. This efficacy interim analysis is for administrative purposes and is not intended to lead to an early termination of the trial if efficacy results appear favorable in a particular treatment arm.

The members, roles, responsibilities, and communication processes of the JMC will be outlined in a separate charter.

6.8.2 Optional Interim Analysis

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct an additional interim efficacy analysis. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and reviewed by the JMC and will follow the communication plan described in the JMC charter.

In addition, the Medical Monitor may request additional safety analysis and may call for additional meetings of the JMC to review ongoing data to assess risk/benefit.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. 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 a Data Quality Plan that describes the quality checking to be performed on the data. Electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 GENERAL ETHICAL CONSIDERATIONS

All patients in this study will receive paclitaxel chemotherapy, given that paclitaxel has been extensively tested in multiple clinical trials for breast cancers in neoadjuvant, adjuvant and metastatic settings and represents an internationally recognized appropriate treatment for this disease. An important aspect of neoadjuvant therapy in TNBC is to decrease tumor size, allowing for breast conservation surgery; in addition, pCR following neoadjuvant chemotherapy is prognostic of favorable long-term outcome. An important consideration for neoadjuvant regimen is good tolerability, allowing completion of the regimen and safe surgical resection.

Taxane-based therapy can improve pCR in the neoadjuvant setting. In addition, single-agent taxane therapy is safer relative to multidrug combinations, exhibiting lower frequency of Grade 3 and 4 events, and lower treatment discontinuation rate (see Section 3.3.3). Notably, only a limited number of patients achieve pCR; thus there is a need for safe and effective regimen in early TNBC (as well as within biomarker subsets of TNBC).

8.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the

ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.3 INFORMED CONSENT

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

A separate sample Research Informed Consent Form that addresses the use of remaining mandatory samples for optional exploratory research will be provided to each site. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not sign the Research ICF.

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

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

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

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

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

8.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

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

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

8.5 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.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Biologic samples obtained in this study will be identified using unique patient identifiers and sample identification numbers. Samples will be linked with clinical data in the clinical database using the sample identification number.

This clinical research involves the procurement of samples of blood and tissue for tumor DNA testing (e.g., mutational status of PIK3CA) as well as genomic DNA testing (e.g., polymorphisms in genes related to metabolic enzymes). DNA samples will not be identified with patients' names, pictures, or any government-issued identification numbers (e.g., Social Security numbers). Samples will be identified using unique sample identification numbers only, which are considered patient identifiers under the Health Insurance and Portability and Accountability Act (HIPAA). Samples will be linked with clinical data in Genentech's clinical study database (including outcome data) by the patient's year of birth and by the study identification number.

8.6 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 (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech and will be managed by Genentech and SOLTI (a cooperative group located in Spain). The SOLTI group will provide clinical operations management in Spain and potentially in Portugal. Approximately 30 U.S. and international sites will participate to enroll approximately 150 patients.

A JMC will be in place during the study and will provide oversight of safety (see Section 3.1.2).

An IWRS will be used to assign screening numbers, randomize patients, monitor enrollment and patient status, and to manage ipatasertib and placebo inventory, requests, and shipments.

Patient data will be recorded via an EDC system from [redacted] using eCRFs (see Section 7).

Central laboratories, including Genentech and Genentech's collaborators, will be used for PIK3CA mutation detection and/or PTEN status determination and will provide kits for PK, tissue, whole blood, and plasma sample analyses to be conducted at central laboratories or Genentech. PTEN evaluation will be conducted prior to randomization, and the results will be used for stratification.

Treatment decisions will be based on local reading of ECGs obtained during the study.

An independent radiologic review facility will be used for the purpose of collecting and assessing the quality of patient imaging scans throughout the trial. The review facility will retain copies of scans for potential centralized assessments of MRI-related endpoints.

9.5 PUBLICATION 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, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Assessments

Assessment	Screening [a]	Cycle 1				Cycle 2				Cycle 3				Pre-surgery	Surgery [b]	Post-surgery [c]	Early Termination Visit [d]
Day	−28 to −1	1	8	15	22	1	8	15	22	1	8	15	22				
Week		1	2	3	4	5	6	7	8	9	10	11	12	~10-12	~14−19	~ ≤4 Weeks	
Signed informed consent	x																
Medical history and demographics	x																
Cancer-related medications and surgical procedures	x															x	
Complete physical examination [e]	x															x	x
Targeted physical examination [f]		x				x				x				x			
Weight	x					x				x						x	
Height	x																
Vital signs [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
ECOG performance status	x					x				x						x	x
Hematology [h]	x	x [i]	x	x	x	x [i]				x [i]				x		x	x
INR, PT, and aPTT/PTT	x													x		x	x
Fasting serum chemistry [j]	x	x [i]				x [i]				x [i]				x		x	x
Fasting lipid profile, amylase	x															x	x
HbA_{1c}	x															x	x
Urinalysis	x					x				x							
Pregnancy test [k]	x					x				x							

Appendix 1
Schedule of Assessments (cont.)

Assessment	Screening [a]	Cycle 1				Cycle 2				Cycle 3				Pre-surgery	Surgery [b]	Post-surgery [c]	Early Termination Visit [d]
Day	–28 to –1	1	8	15	22	1	8	15	22	1	8	15	22				
Week		1	2	3	4	5	6	7	8	9	10	11	12	~10-12	~14–19	~ ≤4 Weeks	
12-lead ECG [l]	x													x			
Mandatory tumor tissue	x [m]		x [m]											x [n]	x [o]		
Optional tumor biopsy [p,q]																	x [r]
Circulating tumor DNA [r]	x [r]									x [r]				x [r]			x [s]
Breast MRI [s]	x													x [s]			x
Breast mammogram [t]	x [t]																
pCR determination															x [o]		
PK sample [u]		x [u]	x [u]														
Whole blood for DNA analysis		x															
Concomitant medications [v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [w, x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Paclitaxel administration		x	x	x	x	x	x	x	x	x	x	x	x				
Fasting insulin	x																
Ipatasertib/placebo dispensation [y]	See footnote [s]																

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin-embedded; HbA_{1c} = glycosylated hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; pCR = pathologic complete response; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time.

Appendix 1
Schedule of Assessments (cont.)

Notes: Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within the screening window (Days −28 to 1) may be used for the study. Screening assessments are to be performed within 28 days preceding Cycle 1 Day 1 unless otherwise noted (e.g., for archival tissue processing, screening assessments may be extended to 8 weeks). Except for Cycle 1 Day 1, all other study visits during the treatment period should be performed within ±3 days of the scheduled date. Screening eligibility labs done within 7 days of Cycle 1 Day 1 may be used for Cycle 1 Day 1 labs. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. All assessments or procedures are to be performed predose unless otherwise specified.

[a] Adequate hematologic and organ function within 14 days before the first study treatment must be determined.

[b] The surgery visit should take place no more than 5 weeks after last dose of paclitaxel.

[c] Perform post-surgery visit approximately within 4 weeks after the surgery.

[d] The early termination visit should occur within 4 weeks after the last administration of ipatasertib or placebo, or paclitaxel, whichever is discontinued last. Note that early termination visit is required only if patients discontinue study treatment prior to protocol specified treatments.

[e] The clinical breast examination and regional lymph node examination shall be performed as part of both the complete physical examination and targeted physical examination.

[f] The clinical breast examination and regional lymph node examination shall be performed as part of both the complete physical examination and targeted physical examination.

[g] Includes heart rate, systolic and diastolic blood pressure while patient is in a seated position after resting for at least 5 minutes; respiratory rate; and oral, axillary, or tympanic and temperature. On paclitaxel dosing days, vital signs to be recorded prior to dosing and at the end of the infusion.

[h] Includes RBC count, WBC count, WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells), absolute neutrophil count, hemoglobin, hematocrit, and platelet count.

[i] Measured prior to dosing.

[j] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN/urea, creatinine, calcium, phosphorus, magnesium, total bilirubin, total protein, albumin, LDH, ALT, AST, and alkaline phosphatase.

[k] For women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile. Screening pregnancy test must be within 14 days of planned cycle day 1. In addition pregnancy tests (serum or urine) are to be performed within approximately 3 days of Day 1 of each treatment cycle ≥Cycle 2, and a pregnancy test should also be performed when clinically indicated. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.

[l] Triplicate 12-lead ECG measurements.

[m] Archival tissue (either FFPE tumor specimens or minimum of 10 unstained paraffin slides) and an associated pathology report must be confirmed to be available prior to entry into the study. If archival tissue is either insufficient or unavailable, FFPE core sample from a pretreatment biopsy of the tumor may be used. FFPE and non-FFPE samples will be prepared from newly collected (fresh) tumor biopsies and surgical resection. All patients must consent to the collection of newly collected tumor biopsies (frozen and FFPE) for PTEN Akt-pathway testing and other biomarker assessments at baseline, Cycle 1 Day 8, and at surgery. At least one FFPE core needle biopsy and at least two

Appendix 1
Schedule of Assessments (cont.)

freshly frozen OCT core needle biopsies are required at baseline and Cycle 1 Day 8 (Week 2).

[n] Patients with significant residual or progressive disease can either proceed directly to surgery or be discontinued from the study, based on the investigator's decision. Patients who will receive additional systemic therapy prior to surgery are required to have an additional research biopsy.

[o] FFPE tumor block/slides from surgical resection (at approximately Weeks 14–19) is required for local assessment of pCR; in addition block/slides are required for analysis of pathway biomarkers by the Sponsor. If a tumor block/slides cannot be obtained for various reasons (e.g., the tumor tissue is not sufficient at surgical resection), the site should discuss with the Sponsor.

[p] Tumor biopsy collection at disease progression is optional and only for patients who provide specific consent, one FFPE tumor biopsy will be collected.

[q] All biopsies collected for study purposes, whether it is required or optional, should be from safely accessible tissue and be minimally invasive.

[r] Blood will be collected for ctDNA analysis at screening, on Cycle 3 Day 1, at the pre-surgery visit, and at the study drug discontinuation or early termination visit.

[s] MRI evaluation is mandatory at screening, pre-surgical visit (approximately weeks 10–12), early termination visit, as well as in cases where disease progression is suspected. MRI scans will be centrally collected and held.

[t] Mammography evaluation at baseline is mandatory if not already acquired as per standard of care between 90 days prior to screening and Day 1.

[u] PK samples should be collected on Cycle 1, Days 1 and 8. See Appendix 2 for schedule of PK assessments.

[v] At screening and Day 1 of Cycle 1, record all concomitant medications taken between 28 days prior to screening and Day 1, Cycle 1; at subsequent timepoints, record new concomitant medications and any changes to the daily dosing.

[w] Record serious adverse events, adverse events leading to ipatasertib, placebo, or paclitaxel discontinuation, and protocol-defined selected adverse events

[x] Patients with an unresolved adverse event or serious adverse event will be followed until the event is resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the event.

[y] Patients will take ipatasertib/placebo on Days 1–21 every 28 days of all cycles. Dispense a sufficient number of ipatasertib/placebo tablets to last until the next visit and provide a medication diary. Extra study drug may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., because of inclement weather or distance of patient's home from study center). Instruct patient to record the time and date they take each study drug dose in the diary and to return all unused study drug at each study visit to assess compliance. Collect and review medication diary, collect unused tablets, and assess compliance at each subsequent visit.

Appendix 2
Schedule of Pharmacokinetic Assessments

Plasma samples for GDC-0068/placebo concentration measurement will be collected in Cycle 1 only. The following information will need to be captured to allow PK analysis:

1. Actual dose amount, dose time, and sampling time on Day 1
2. Actual dose amount and dose time on the previous day
3. Actual dose amount and dose time on the day of sampling (e.g., if the PK sampling occurs on Day 7, the dose time will need to be collected on Day 6 and on Day 7)
4. Actual sampling times at each sample collection

Study Visit	Sampling Time Window
Cycle 1, Day 1	0.5 to 2 hours post−GDC-0068/placebo
	4 to 6 hours post−GDC-0068/placebo
Cycle 1, Day 8	0 to 2 hours prior to GDC-0068/placebo
	2 to 5 hours post−GDC-0068/placebo

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors: Assessment of Response of Neoadjuvant Therapy in Early Breast Cancer

Conventional response criteria may not be ideal for the assessment of response in the setting of neoadjuvant therapy in early breast cancer. Therefore, RECIST 1.1 criteria have been modified to specifically address assessment of primary breast lesions along with axillary lymph node disease, using a range of breast imaging modalities. Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with modifications and the addition of explanatory text as needed for clarity. For detailed information on the read methodology including how imaging data should be processed prior to reads, please refer to the Study Imaging Charter.

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

CT = computed tomography; MRI = magnetic resonance imaging; SAD = short axis dimension.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

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

Method of Measurement

According to RECIST 1.1 guidelines, MRI is the preferred modality to follow breast lesions in a neoadjuvant setting. CT is currently the preferred modality for assessing metastatic disease, but should not be used in this focused setting of neoadjuvant

[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.

therapy in early breast cancer. Ultrasound, mammography, and clinical exam are all common and useful modalities for assessing breast lesions, and will also be used to assess response in this protocol, adhering to response criteria as presented in this appendix.

Target Lesions

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

Bilateral breast imaging studies should be conducted at each study assessment. The same method of measurement and the same technique should be used to characterize each target lesion at baseline and during the study, and all measurements should be recorded in metric notation. Care must be taken in measurement of target lesions with different modalities, since the same lesion may appear to have a different size with each modality. If for some reason the same imaging modality cannot be used at a scheduled assessment time point, then the case should be discussed with the radiologist to determine if substitution of any other approach is possible and, if not, the patient should be considered not evaluable at that timepoint, for that particular type of imaging assessment.

Non-Target Lesions

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

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Axillary lymph nodes are known to vary widely in size, and signs of abnormality in axillary lymph nodes on imaging include other morphological findings often in addition to changes in nodal size. For these reasons, pathologic axillary lymph nodes on imaging should be identified as

non-target lesions at baseline. Change in short-axis dimension may be considered in the assessment of pathology, but measurements are not required, and these lesions should be followed qualitatively, as described below at each response assessment timepoint.

Signs of lymph node pathology on imaging include the following:

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

EVALUATION OF RESPONSE

Evaluation of Target Lesions

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

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

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors: Assessment of Response of Neoadjuvant Therapy in Early Breast Cancer (cont.)

Special Notes on the Assessment of Target Lesions

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

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

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

Evaluation of Non-Target Lesions

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

- CR: disappearance of all non-target lesions
  - All lymph nodes must be non-pathologic in appearance
- Non-CR/Non-PD: persistence of one or more non-target lesion(s)
- PD: unequivocal progression of existing non-target lesions. For pathologic axillary lymph nodes, this may be based on a combination of morphological factors, including a potential increase in short-axis dimension

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors: Assessment of Response of Neoadjuvant Therapy in Early Breast Cancer (cont.)

Special Notes on Assessment of Progression of Non-Target Disease

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

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a breast lesion may be reported on an MRI scan report as a "new" cystic lesion, which it is not. A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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

Timepoint Response (Overall Response)

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

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors: Assessment of Response of Neoadjuvant Therapy in Early Breast Cancer (cont.)

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

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

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

Missing Assessments and Not-Evaluable Designation

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

Special Notes on Response Assessment

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

Appendix 4
ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 5
New York Heart Association Classification of Functional Cardiac Capacity

Class	Description
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix 6
Management Guideline for Diarrhea

General	• Instruct patients to promptly contact investigators if they develop diarrhea (even mild) • Exclude patients with active inflammatory bowel diseases, Crohn's disease or ulcerative colitis • Rule out Infectious or alternate etiologies (e.g., inflammatory colitis) • Gr≥3 colitis is protocol-defined AESI • Any Gr≥3 diarrhea, or Gr≥2 diarrhea persisting for >5 days despite optimal medical management[a] /dose hold, inform Medical Monitor (protocol-defined AESI)	
Treatment Recommendations	• Initiate anti-diarrheal [a] and supportive therapy [b] AT FIRST REPORT • Dose reduction should occur only if diarrhea persist despite optimal medical treatment • If ipatasertib/placebo treatment is delayed, paclitaxel treatment should continue. • If Gr 1 diarrhea persists following two dose reductions of ipatasertib/placebo, consider prophylaxis or a treatment hold including ipatasertib/placebo and paclitaxel. Dose intensity for paclitaxel should be maintained as much as safely possible	
	AE Management	**Ipatasertib/Placebo Dose Modification**
Grade 1 Increase of <4 stools per day; mild increase	•Adequate treatment with anti-diarrheals [a] •Maximum supportive care [b] •Close monitor for resolution •Prophylaxis may be considered [c]	• None
Grade 2 Increase of 4 - 6 stools per day; Moderate increase	• Adequate treatment with anti-diarrheals [a] • Maximum supportive care [b] • Close monitor for resolution • Prophylaxis should be considered [c]	• Interrupt until recovery to Gr ≤ 1 • May be resumed at the same dose • If recurs, reduce by one dose level
Grade ≥ 3 Increase of >=7 stools per day; incontinence; hospitalization indicated; severe Increase, limiting self care ADL	• Adequate treatment with anti-diarrheals [a] • Maximum supportive care [b] • Close monitor for resolution • Prophylaxis should be considered [c]	• Interrupt ipatasertib until recovery to Gr ≤ 1 • Reduce ipatasertib by one dose level • If recurs, reduce ipatasert b by one dose level

(a) Treatment at any first report of diarrhea
- Initiate loperamide (Imodium) dose with 4 mg, then 2 mg after each loose stools, not to exceed 16mg in any 24-hour period
- May consider using combination of loperamide and Lomotil (diphenoxylate and atropine) if available
- May initiate 2nd line therapy (including but not limited to codeine or octreotide) per local guidelines and standard of care, if Gr≥2 diarrhea persists after 48 hours of treatment with loperamide and/or Lomotil (if available). Discuss with Medical Monitor the use of any other standard anti-diarrheal as per local guidelines.

(b) Supportive care
- Dietary modification: Stop all lactose-containing products and eat small meals; encourage adequate hydration with salt-containing liquids such as broth or Gatorade
- Initiate appropriate hydration therapy and electrolyte supplements when clinically indicated

(c) Prophylaxis
- For Patients who had Gr≥2 diarrhea and resolved to Gr ≤ 1, continued dosing of loperamide (i.e. prophylaxis dosing at 2mg, 2-4 times daily) should be considered and may be considered for patients who experience persistent Grade 1 diarrhea