**Document Type:** Protocol and Amendments

**Official Title:** A Phase II Randomized, Double-Blind Study of Neoadjuvant Letrozole Plus GDC-0032 Versus Letrozole plus Placebo in Postmenopausal Women with ER-positive/HER2-negative, Early Stage Breast Cancer

**NCT Number:** NCT02273973

**Document Date:** Protocol Amendment Version 4: 27-July-2015

Protocol Amendment Version 3: 22-May-2014

Protocol Amendment Version 2: 09-Apr-2014

Protocol Amendment Version 1: 23-Dec-2013

# PROTOCOL

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| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2-NEGATIVE, EARLY STAGE BREAST CANCER** |
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38/ NCT02273973 |
| **VERSION NUMBER:** | 4 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | *121658* |
| **TEST PRODUCT:** | GDC-0032 |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.D. |
| **SPONSOR:** | Genentech, Inc. |
| **DATE FINAL:** | Version 1: 23 December 2013 |
| **DATES AMENDED:** | Version 2: 9 April 2014<br>Version 3: 22 May 2014<br>Version 4: See electronic date stamp below. |

| **Approver's Name** | **Title** | **Date and Time (UTC)** |
|---|---|---|
| [redacted] | [redacted] | 27-Jul-2015 20:27:55 |

## PROTOCOL AMENDMENT APPROVAL

## PROTOCOL AMENDMENT, VERSION 4: RATIONALE

The following changes have been made in this amendment:

- Adverse Event of Special Interest (AESI) Grade ≥3 diarrhea has been changed to Grade ≥2 diarrhea
- Grade ≥1 diarrhea that persists for more than 2 weeks despite antidiarrheals (e.g., loperamide) has been added as an AESI
- Recommendation to Management of Gastrointestinal Toxicities that patients experiencing Grades ≥1 diarrhea be contacted at least weekly (e.g., by telephone) has been added
- Adverse Event assessments at Weeks 7 and 11 by telephone have been added for a general assessment of adverse events

*Rationale*: The above changes were prompted by the number of suboptimally managed cases of diarrhea, one of which resulted in colitis. These changes, including the addition of adverse event assessments at Weeks 7 and 11, have been made to increase monitoring of diarrhea.

Other changes are as follows:

- Added collection of additional blood sample at 4-week Post-Surgical Follow-Up visit for ctDNA and plasma protein biomarkers analysis.

  *Rationale*: This is aimed to enable correlation of response with biomarkers and potential identification of high-risk population(s)

- Requirement added for Target Lesion #2, if selected, to be ≥10 mm.

  *Rationale*: No minimum size was previously defined; therefore, this change was made to improve clarity.

- Added additional restriction to the following exclusion criterion: "History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis). *Any patient with a baseline medical condition involving the gastrointestinal (GI) tract or who may have a predisposition for GI toxicity requires prior approval from the Medical Monitor*."

  *Rationale*: This was added with the intention that it may further prevent patients with potential predispositions to GI side effects from being enrolled.

- Included "Investigational Agents" amongst prohibited Concomitant Therapies.

  *Rationale*: This was not previously specified; therefore, this change was made to improve clarity.

- Added specification that there is a 4-week "wash-out" period for any other Investigational Agents prior to initiation of treatment with GDC-0032.

  *Rationale*: This was not previously specified; therefore, this change was made to improve clarity

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 4:**
**SUMMARY OF CHANGES**

## GLOBAL CHANGES

Non-serious has been deleted from "non-serious adverse event of special interest" throughout the protocol.

IND number has changed from 110184 to 121658

Medical Monitor has changed from [redacted] to [redacted], M.D. Ph.D.

## PROTOCOL SYNOPSIS

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

## LIST OF AUTHORS

[redacted], and [redacted] were added and [redacted] was removed from the list.

## SECTION 1.3: BACKGROUND ON THE PI3K/AKT/MTOR PATHWAY AND BREAST CANCER

Genes in the PI3K/AKT/mTOR signaling pathway are frequently mutated or amplified in breast cancer, especially in the ER+ subtype (Cancer Genome Atlas Network [CGAN] 2012). Molecular alterations of the PI3K/AKT/mTOR pathway include the following: (1) Mutations or amplifications in *PIK3CA*, the gene encoding the alpha catalytic subunit of PI3K (p110$\alpha$) (Saal et al. 2005; Wu et al. 2005); (2) Alterations in the tumor suppressor gene *PTEN*, either by loss of protein expression (PTEN null), inactivation mutations and/or epigenetic deregulation through promoter hypermethylation (García et al. 2004); (3) PDKP1 amplification and/or overexpression (Brugge et al. 2007); (4) AKT1 somatic *gain-of*-function mutations (Stemke-Hale et al. 2008) and AKT2 amplifications (Bellacosa et al. 1995). Overall, it is estimated that up to 70% of breast cancers can have some form of molecular aberration of the PI3K/AKT/mTOR pathway (CGAN 2012).

## SECTION 1.4: BACKGROUND ON REVERSING HORMONAL RESISTANCE BY INHIBITING THE PI3K/MTOR/AKT PATHWAY

In the setting of ER+ breast cancer, *the* PI3K *signaling pathway* seems to play an important role in mediating hormonal resistance and is a viable therapeutic target. Hyperactivation of this signaling pathway was proved to promote both *de novo* *(primary)* and acquired *(secondary)* resistance to hormone therapy in ER+ breast cancer cell lines and xenograft models (Sabnis et al. 2007)~~, and~~. ~~simultaneous~~ *Simultaneous* blocking of the PI3K/AKT/mTOR pathway with everolimus*, an mTOR inhibitor,* and the ER pathway with letrozole enhances antitumor activity of either agent alone (Boulay et al. 2005). Importantly, a baseline protein signature of PI3K activation was found to be predictive of a poor prognosis after adjuvant endocrine therapy (Miller et al. 2010).

In the clinical setting, impressive results of the combination of exemestane and everolimus~~, an mTOR inhibitor,~~ were reported in the BOLERO-2 trial (Baselga et al. 2009).…

## SECTION 1.5: BACKGROUND ON NEOADJUVANT THERAPY IN BREAST CANCER

…In September 2013, the Food and Drug Administration (FDA) granted accelerated approval of *pertuzumab (*Perjeta®*)* as part of a complete treatment regimen for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer in the neoadjuvant setting.

## SECTION 1.6: BACKGROUND ON GDC-0032

GDC-0032 has demonstrated activity in *preclinical* models of *PIK3CA*-mutant breast tumors in vivo as a single agent and in combination with standard of care (e.g., paclitaxel or docetaxel) or endocrine therapies (e.g., letrozole or fulvestrant).…

## SECTION 3: STUDY DESIGN

*In addition to the safety assessments conducted at the scheduled follow-up visits, patients will be contacted by telephone for a general assessment of adverse events at Weeks 7 and 11.*

Blood sample*s* for exploratory endpoint analysis will be collected on Day 1 prior to dosing, at Week 9, ~~and~~ prior to surgery *(Week 16 visit,) and at the 4-weeks postsurgical follow-up visit*.

## SECTION 3.3.1: Rationale for Conducting the Study in the Neoadjuvant Setting

…Known as the intrinsic subtypes of breast cancer, these groups of tumors have revealed critical differences in incidence, survival, and response to treatment *(Sotiriou et al. 2003)*. As genomic studies evolve, further sub-classifications of breast tumors are expected to emerge. Thus, a major challenge in breast cancer management is how to prospectively select patients who will derive the maximum benefit from a given drug regimen and minimizing unnecessary toxicities for patients with non-responsive disease.

## SECTION 3.3.3: Rationale for Control Group

The *Immediate Preoperative Anastrozole, Tamoxifen, or Combined With Tamoxifen (*IMPACT*)* trial was a randomized, Phase II, double-blind, double-dummy, multicenter trial that randomly assigned 330 postmenopausal women with ER+ operable or locally advanced, potentially operable breast cancer in a 1:1:1 ratio to receive a daily dose of anastrozole 1 mg and tamoxifen placebo, tamoxifen 20 mg and anastrozole placebo, or a combination of tamoxifen 20 mg and anastrozole 1 mg for 12 weeks before surgery.…

The *American College of Surgeons Oncology Group (*ACOSOG*)* Z1031 trial compared three AIs in a randomized, Phase II, neoadjuvant trial designed to select agents for Phase III investigations.…

### SECTION 3.3.4.1: Rationale for Efficacy Outcome Measure of Pathologic Complete Response

In trials of neoadjuvant hormonal therapy, pCR is an unlikely event. For instance, in the neoadjuvant trial comparing everolimus plus letrozole to letrozole *plus placebo*, pCR rates were 1.4% and 0.8%, respectively (Baselga et al. 2009).

In September of 2013, the FDA granted accelerated approval of *pertuzumab (*Perjeta®*), an HER2 dimerization inhibitor,* as part of a complete treatment regimen for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer in the neoadjuvant setting.

### SECTION 3.3.7: Rationale for GDC-0032 Dosage

As of 5 July 2013, 34 patients have been enrolled into the dose-escalation stage of Study PMT4979g, and 56 patients have been enrolled into the single-agent expansion cohorts at 9 mg in Stage 2 (Cohorts A-D and G). All patients received GDC-0032 in capsules. Five dose-escalation cohorts (i.e., 3, 5, 8, 12, and 16 mg daily) were tested (see Section 1.7.1). The maximal administered dose was 16 mg. To obtain more safety data on long-term tolerability, the recommended single-agent dose and schedule for the single-agent GDC-0032 expansion stage ~~is~~ *was* 9-mg *capsules* daily.

Of the 19 efficacy-evaluable patients treated with GDC-0032 in combination with letrozole, one patient at 6 mg *capsule* had a cPR. The *PIK3CA* mutation status of this patient is unknown. Since efficacy has been observed at 6 mg *capsules*, and the long-term safety suggests that 6 mg *capsule* is better tolerated, the neoadjuvant study will utilize 6-mg GDC-0032 *capsules* in combination with letrozole.

Of the 27 efficacy-evaluable patients treated with GDC-0032 in combination with fulvestrant, 2 confirmed partial responses were observed at 6 mg *capsules* and 1 confirmed partial response at 9 mg *capsules*.

Colitis has been observed with an incidence rate of 6.2% (10/160 patients). The time (from the first dose of study treatment) to onset of colitis ranged from approximately 82–248 days as either a single agent or in combination with letrozole or fulvestrant. Most of the colitis cases have been observed at the 9-mg *capsule* dose level or higher. To mitigate ~~the~~ late-onset adverse events, such as colitis, an intermittent dosing schedule will be applied. With the 40-hour half-life, a limited impact on efficacy is anticipated.…

### SECTION 3.3.8: Rationale for Biomarker Assessments

Next generation sequencing (NGS) techniques, like deep genome sequencing, may offer a unique opportunity to identify such biomarkers of response. For example, using whole

genome sequencing, a two base-pair deletion in the *tuberous sclerosis 1 (TSC1)* gene was found in a patient with metastatic bladder cancer with a prolonged response (>2 years) to everolimus as single agent (Iyer et al. 2012). Among 13 additional patients with bladder cancer treated with everolimus in the same trial, those with *TSC1* mutant tumors remained on therapy longer than those with WT tumors (7.7 vs. 2.0 months, p=0.004), suggesting that mTORC-1 directed therapies may be most effective in patients with cancer whose tumors harbor *TSC1* somatic mutations. *Furthermore, interesting data was recently reported from an autopsy case study from a patient with metastatic breast cancer that received an alpha-isoform PI3K blocking agent and succumbed to her disease after a lasting clinical response (Juric et al. 2015). Extensive metastatic sampling was performed post-mortem, with the main finding being the emergence of molecular aberrations leading to loss of PTEN; thus, indicating a new mechanism of secondary resistance to PI3K blockade.* Similar approaches could be of great value when analyzing responses to agents targeting the PI3K/AKT/mTOR pathway, especially in the neoadjuvant setting.

## SECTION 4.1.2: Exclusion Criteria

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

- History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis). *Any patient with a baseline medical condition involving the gastrointestinal (GI) tract or who may have a predisposition for GI toxicity requires prior approval from the Medical Monitor.*

## SECTION 4.5.10: Laboratory Assessments

The following assessments will be performed at the local laboratory. The frequency of assessments is provided in Appendix 1.

- Hematology (complete blood count, including red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with differential [neutrophils, eosinophils, basophils, lymphocytes, monocytes, and other cells, *if applicable*]), and platelet count.

The following assessments will be performed at a central laboratory. Instruction manuals outlining sampling procedures, storage conditions, and shipment instructions and supply kits will be provided for all central laboratory assessments:

- Tumor tissue should be *from the primary tumor (not lymph nodes) and* of good quality based on total and viable tumor content. Evaluation of the patient's tumor sample for adequate tumor tissue content by a central laboratory must occur prior to initiation of study treatment. A minimum of ten unstained slides from a prior diagnostic FFPE core biopsy would be required for enrollment eligibility purposes.

  A formalin-fixed, paraffin-embedded tumor block from surgical resection (Weeks 17–18) is required. If a tumor block cannot be obtained for various reasons (e.g., the tumor tissue is not sufficient at surgical resection), the site should discuss with the central study team. In such cases, paraffin-embedded, unstained slides (a minimum of 20 and up to 40 unstained slides) from a

surgical specimen are required at surgery (Weeks 17–18). *Except in the case of pCR, every effort should be made to obtain a fresh-frozen tumor tissue sample at surgery.*

### SECTION 4.5.11.1: Mutational Analysis for *PIK3CA*

Somatic mutations in the *PIK3CA* gene are found in approximately 35%–40% of ER-positive breast cancers and occur most commonly in Exons 9 and 20 *(helical and kinase domain, respectively)* in the codons encoding amino acids E542, E545, and H1047 (Saal et al. 2005).…

### SECTION 5.1.1.3: Management of Rash

Rash and other dermatological events should be closely monitored, and patients with severe rash should be monitored for associated signs and symptoms such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. For severe rash, dosing of GDC-0032*/placebo* should be interrupted, and patients should be treated with supportive therapy per standard of care. Use of antihistamines, as well as topical or systemic corticosteroids, may be considered (see Table 4).

### SECTION 5.1.1.4.1: Management of Diarrhea and Colitis

Patients should be closely monitored for gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain, stomatitis, and changes in stool, including checking for blood in stool if clinically indicated). Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. *Weekly patient contact (e.g., telephone call) for all events of diarrhea Grades ≥1 is recommended to closely follow until resolution of symptoms.* Gastrointestinal symptoms should be managed per protocol guidelines and institutional standard of care. For example, prompt management of diarrhea with antidiarrheal medications should be implemented. Because of the approximately 40-hour half-life of GDC-0032, investigators should hold GDC-0032*/placebo* for Grade ≥2 diarrhea.

Perforated duodenal ulcer has been observed in 2 patients (one patient at 6 mg *capsule* in combination with letrozole; another patient at 6 mg *capsule* in combination with fulvestrant). Appropriate caution should be taken with the administration of medications such as aspirin, nonsteroidal anti-inflammatory drugs, and corticosteroids that can increase the risk of gastritis, peptic ulcers, or gastrointestinal perforation.

### SECTION 5.2.3: ~~Non Serious~~ Adverse Events of Special Interest (Immediately Reportable to ABCSG)

~~Non serious a~~*A*dverse events of special interest are required to be reported by the investigator to ABCSG safety department 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:

- Grade ≥ ~~3~~ *2* diarrhea

- *Grade ≥1 diarrhea for >2 weeks after following medical management guidelines in Section 5.1.1.4*

## SECTION 5.4.1: Emergency Medical Contacts

Genentech's Medical Monitor Contact Information:

Medical Monitor: [redacted], M.D., Ph.D.

Telephone No. [redacted]

## SECTION 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. *With regard to the adverse event of special interest of diarrhea, it is recommended that investigators follow every adverse event of ≥Grade 1 diarrhea with weekly patient contacts (e.g., telephone calls) and follow up until resolution. Cases that do not resolve within 1–2 weeks should be aggressively managed per protocol recommendations for gastrointestinal toxicities.*

## SECTION 5.6: POST-STUDY ADVERSE EVENTS

The investigator should report these events ~~by completing and faxing a paper Serious Adverse Event Reporting Form and fax cover sheet to Safety Risk Management using the fax numbers provided to investigators~~ *directly to the Sponsor 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.* (see "Protocol Administrative and Contact Information & List of Investigators").

## SECTION 6.1: DETERMINATION OF SAMPLE SIZE

To control an overall, two-sided, family-wise error rate under 20% *for each analysis population*, we use a two-sided significance level of 16% and 4% for the co-primary endpoints MRI ORR, and pCR, respectively.

## SECTION 6.4.1: Primary Efficacy Endpoint

…The pCR rate will also be calculated and compared at a two-sided alpha of 4% based on the same analytical approach as ORR. The two alpha values account for a family-wise type I error rate of 20% *for each analysis population*. Patients with early study termination and hence missing efficacy outcome will be considered as non-responders.

## TABLE 2: Dose Modification and Management Guidelines for Hyperglycemia (Based on Fasting Blood Glucose)

Table 2 has been updated to include placebo throughout: GDC-0032*/placebo.*

**TABLE 3: Dose Modification and Management Guidelines for Pneumonitis**

Table 3 has been updated to include placebo throughout: GDC-0032*/placebo.*

**TABLE 4: GDC-0032 Dose Modification and Management Guidelines for Rash**

Table 4 has been updated to include placebo throughout: GDC-0032*/placebo.*

**TABLE 5: GDC-0032 Dose Modification and Management Guidelines for Diarrhea and Colitis**

Table 5 has been updated to include placebo throughout: GDC-0032*/placebo.* The following was also added to the table: *For any grade of diarrhea (≥1), contact patient at least weekly to monitor until resolution of symptoms. If symptoms persist beyond 2 weeks despite antidiarrheal treatment (e.g., loperamide), escalate to Grade 2 management.*

**TABLE 6: GDC-0032 Dose Delay and Modification Guidelines for Stomatitis and Oral Mucositis**

Table 6 has been updated to include placebo throughout: GDC-0032*/placebo.*

**TABLE 7: GDC-0032 Dose Delay and Modification Guidelines for Other Clinically Significant Adverse Events**

Table 7 has been updated to include placebo throughout: GDC-0032*/placebo.*

**APPENDIX 1: Schedule of Assessments**

The Schedule of Assessments has been revised to reflect the changes to the protocol.

**APPENDIX 3: MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: ASSESSMENT OF RESPONSE OF NEOADJUVANT THERAPY IN EARLY BREAST CANCER**

**Target Lesions**

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should lend themselves to reproducible repeated measurements. Up to 2 lesions in the breast may be identified as target lesions. *Per this protocol, target lesion #1 must be ≥2 cm and, if selected, target lesion #2 must be ≥10 mm.*

**SAMPLE INFORMED CONSENT FORMS**

The sample Informed Consent Forms have been revised to reflect the changes to the protocol.

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| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38 |
| **VERSION NUMBER:** | 4 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | *121658* |
| **TEST PRODUCT:** | GDC-0032 |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.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 return the signed original of this form as instructed by your local study monitor. Please retain a copy for your study files.

**Principal Investigators:**

[redacted]

| Author(s): | Affiliation |
|---|---|
| [redacted] | [redacted], USA<br>[redacted], Belgium<br>[redacted], SOLTI Breast Cancer Research Group, Diputació 256 4º1ª 08007 Barcelona, Spain<br>[redacted], Genentech, South San Francisco, CA, USA<br>[redacted], ABCSG, Nussdorfer Platz 8, 1190 Wien, Austria<br>[redacted], ABCSG, Nussdorfer Platz 8, 1190 Wien, Austria<br>[redacted], ABCSG, Austria<br>[redacted], Genentech, South San Francisco, CA, USA<br>*[redacted], Genentech, South San Francisco, CA USA*<br>[redacted] Spain<br>[redacted] Spain<br>[redacted], Belgium<br>[redacted], Spain<br>*[redacted], Genentech, South San Francisco, CA USA*<br>*[redacted], Genentech, South San Francisco, CA USA*<br>*[redacted], SOLTI Breast Cancer Research Group, Diputació 256 4º1ª 08007 Barcelona, Spain*<br>[redacted], Spain<br>*[redacted], Belgium* |

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2- NEGATIVE, EARLY STAGE BREAST CANCER** |
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| **IND NUMBER:** | *121658* |
| **TEST PRODUCT:** | GDC-0032 |
| **PHASE:** | II |
| **INDICATION:** | Early stage breast cancer |
| **SPONSOR:** | Genentech, Inc. |

### Objectives

#### Efficacy Objectives

The primary objective of this study is to evaluate the efficacy of letrozole plus GDC-0032 versus letrozole plus placebo in women with estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2−) early stage breast cancer, as measured by the following co-primary endpoints:

- Tumor overall objective response rate (ORR) by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in all enrolled patients and *PIK3CA* mutant (MT) patients
- Pathologic complete response (pCR) rate in breast and axilla (ypT0/Tis ypN0) by local evaluation in all enrolled patients and *PIK3CA* MT patients

The secondary efficacy objectives of this study are the following:

- Tumor objective response rate (ORR), assessed by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR ypT0/Tis ypN0) by local evaluation in *PIK3CA* wildtype (WT) patients

The following secondary objectives will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of locally assessed ORR as measured by modified RECIST criteria (Appendix 3) using the following methods:
  - Breast ultrasound
  - Clinical breast exam (i.e., palpation)
  - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery.

- Compare the centrally derived, preoperative endocrine prognostic index (PEPI) score upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo.
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment.
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

**Safety Objective**

The safety objective for this study is as follows:

- Evaluate the safety of letrozole plus GDC-0032 versus letrozole plus placebo

**Patient-Reported Outcome Objectives**

The patient-reported outcome (PRO) objectives for this study are as follows:

- Evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23)

**Exploratory Objectives**

The exploratory objectives for this study are as follows:

- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess whether biomarkers from tumor tissue or blood, including but not limited to somatic cancer associated mutations, PTEN expression, pro-survival pathways (such as PI3K/AKT, MAPK etc.), apoptotic markers, and levels of RNA and DNA expression are predictive of response
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to anti-tumor activity
- To assess concordance and percentage of *PIK3CA* mutation status from baseline biopsy and surgical specimen
- To assess emergence of resistance alleles from tumor tissue or blood
- To assess concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response
- To assess the pharmacokinetics and possible drug interaction between letrozole and GDC-0032 upon concomitant administration
- To assess the correlation of GDC-0032 drug levels and GDC-0032 related response (efficacy or adverse events [e.g., colitis, rash])
- To assess the influence of pharmacogenetic polymorphisms on GDC-0032 and/or letrozole on pharmacokinetics and response (either efficacy and/or adverse events)
- Compare the rates of breast-conserving surgery (BCS) and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo.

## Study Design

**Description of Study**

This is a two-arm, randomized, double-blind, multicenter, pre-operative study to evaluate the effect of combining letrozole and GDC-0032 versus letrozole and placebo in postmenopausal women with ER+/HER2− untreated, Stage I-III operable breast cancer whose primary tumors are ≥ 2 cm. Patients with cT4 or cN3 tumors are not eligible. Standard of care assessments/procedures (e.g., bilateral mammogram) performed within 28 days of Day 1 dosing do not need to be repeated for screening purposes.

All patients will undergo pretreatment tumor tissue acquisition (snap-frozen [optimal cutting temperature; OCT] and formalin-fixed paraffin-embedded cores [FFPE]). Two pretreatment FFPE core biopsies and one freshly frozen core biopsy must be obtained for all patients prior to beginning study drug treatment. Prior diagnostic FFPE core biopsies may be used for enrollment eligibility purposes. For the purpose of enrollment, ER, progesterone receptor (PR), and HER2 will be locally determined prior to beginning of study treatment. ER, PR, HER2, and

the percentage of Ki67-positive cells will also be centrally assessed, but the results do not have to be available prior to enrollment in the study. Remaining tissue will be retained for future translational studies. Pre-surgical sentinel lymph node biopsy (SLNB) is not allowed.

Patients will be randomized into one of the two treatment arms with a 1:1 randomization ratio. Letrozole at 2.5 mg will be dosed once daily plus either GDC-0032 at 4 mg (two 2-mg tablets) *or* placebo on a 5–days-on/ 2–days-off schedule for a total of 16 weeks (see Figure 5). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

After confirmation of all the eligibility criteria, patients will be randomized to one of the treatment arms. A second biopsy will be performed on Day 15 (Week 3) for biomarker analyses. Biopsies should be performed at least 2 hours after GDC-0032 dose administration.

Randomization will be stratified according to 2 factors:

1. Tumor size (T1-T2 vs. T3)
2. Nodal status (cytologically positive vs. radiologically or cytologically negative)

The study will enroll approximately 330 patients at approximately 110 global sites.

At Weeks 1, 5, 9, 13, and 16 the primary breast tumor and axillary lymph nodes will be assessed by clinical breast examination (palpation and caliper measurement). Suspicion of progression based on clinical exam at any time should be further evaluated (Figure 6).

*In addition to the safety assessments conducted at the scheduled follow-up visits, patients will be contacted by telephone for a general assessment of adverse events at Weeks 7 and 11.*

At Week 9, a breast ultrasound will be performed to ensure that there is no progressive disease and for the purpose of surgery planning. Suspicion of progressive disease on breast ultrasound should be confirmed by investigator-assessed breast MRI. Patients with primary disease not evaluable by ultrasound at baseline should be assessed by MRI at Week 9. Suspected progression in nodes should also be confirmed by fine needle aspiration (FNA) if these nodes had not been previously shown to be cytologically positive for cancer. Patients with progressive disease (as defined by modified RECIST, Appendix 3), can either proceed directly to surgery or be taken off of the study, according to the investigator's decision. If the patient goes off-study every reasonable effort should be made to obtain a new biopsy sample prior to beginning another systemic treatment.

From Week 13, the patient will visit with the surgeon. The purpose of this visit is two-fold: tentative planning of the type of breast surgery to be performed (breast conservative vs. mastectomy) and scheduling the date for definitive surgery.

During Week 16, breast MRI will be done for the purpose of primary endpoint analysis. Clinical breast exam, breast ultrasound, and mammography will also be conducted prior to surgery for the purpose of the secondary endpoint analysis.

Blood sample*s* for exploratory endpoint analysis will be collected on Day 1 prior to dosing, at Week 9, prior to surgery *(Week 16 visit,) and at the 4-weeks postsurgical follow-up visit*.

**Surgery**

Surgery will take place after at least 16 weeks of treatment, during Weeks 17–18. Surgery should be performed within 4 days after the last dose of GDC-0032, if possible, to best observe pharmacodynamic knockdown with GDC-0032 in the surgical specimen. Surgery may be delayed due to toxicity or other safety issues, upon discussion with the Medical Monitor (see Section 5.4.1) or recommendations from the Independent Data Monitoring Committee (IDMC; see below). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

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. Surgery specimens will be collected for histological examination to assess for pCR and for other endpoint analyses.

Following surgery, follow-up will proceed according to local standards of care. Adjuvant endocrine therapy and/or chemotherapy will be delivered as per the investigator's choice. Postoperative radiotherapy is required if BCS is performed. In the event of mastectomy, radiotherapy is to be administered according to local guidelines.

A postsurgery visit will be performed 4 weeks (+1 week) after surgery, and will mark the end of the study. Assessment of adverse events and general safety will be collected at this visit and the plan for future treatment will be recorded.

The patient should be evaluated at baseline and after Week 13 of treatment for planning the surgical procedure (BCS or mastectomy), and both the planned and actual surgical treatment should be documented in the electronic Case Report Form (eCRF).

The co-primary efficacy endpoint, pathological complete response (pCR–ypT0/is, ypN0) will be established via a local review following completion of neoadjuvant therapy and surgery.

Please refer to the pathology manual for further guidance of evaluation for pCR and directions for sending a copy of the pathology report.

A schedule of assessments is provided in Appendix 1.

An Independent Review Facility (IRF) will be used to determine the tumor ORR via MRI. IRF procedures are detailed in the IRF charter.

**Number of Patients**

The study will enroll approximately 330 patients at approximately 110 global sites.

**Target Population**

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF) prior to any study-specific procedure
- Female patients
- Postmenopausal status and age ≥ 18 years. Postmenopausal status is defined as follows:
  - Age ≥ 60 years or
  - Age < 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment or
  - Prior bilateral oophorectomy (≥ 28 days prior to Day 1 of treatment)
- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor ≥ 2 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 ≥ 2 cm and designated as the "target" lesion for all subsequent tumor evaluations.
  - Stage I to operable Stage III breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms).
- ER-positive and HER2-negative breast cancer, as per local laboratory or regional definition
- Breast cancer eligible for primary surgery
- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for *PIK3CA* mutation status by central histopathology laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Fasting glucose ≤125 mg/dL
- Adequate hematological, renal, and hepatic function, as follows:
  - Absolute neutrophil count ≥ 1500/μL
  - Platelets count ≥100,000/μL
  - Hemoglobin ≥9 g/dL
  - Serum bilirubin ≤1.5 × the upper limit of normal (ULN)

  - Patients with known Gilbert's disease who have serum bilirubin $\leq 3 \times$ ULN may be enrolled
- Aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase $\leq 1.5 \times$ ULN Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq 50$ mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation:

  $$(140 - \text{age}) \times (\text{weight in kg}) \times (0.85)$$
  $$72 \times (\text{serum creatinine in mg/dL})$$
- International normalized ratio (INR) $< 1.5 \times$ ULN and activated partial thromboplastin time (aPTT) $< 1.5 \times$ ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2–3 is required. If anticoagulation is required for a prosthetic heart valve, then INR should be between 2.5–3.5.
- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Ability and willingness to comply with study visits, treatment, testing, and to comply with the protocol, in the investigator's judgment

Exclusion Criteria

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

- Any prior treatment for primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer
- 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 sentinel lymph node biopsy prior to study treatment
- Patients for whom upfront chemotherapy is clinically judged appropriate as optimal neoadjuvant treatment
- Patients for whom immediate surgery is indicated
- Type 1 or 2 diabetes requiring antihyperglycemic medication
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteric absorption
- History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis). *Any patient with a baseline medical condition involving the gastrointestinal (GI) tract or who may have a predisposition for GI toxicity requires prior approval from the Medical Monitor.*
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF) $> 470$ msec
- Diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$) $< 60\%$ of the predicted values (see Appendix 7 for calculations)
- Clinically significant (i.e., active) cardiovascular disease, uncontrolled hypertension, unstable angina, history of myocardial infarction, cardiac failure class II-IV (New York Heart Association, Appendix 5), or any other that in the judgment of the investigator could jeopardize patient safety or study outcomes
- 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
- Active infection requiring intravenous (IV) antibiotics
- Patients requiring any daily supplemental oxygen
- Clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis
- Known human immunodeficiency virus (HIV) infection
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications
- Significant traumatic injury within 3 weeks prior to initiation of study treatment
- Major surgical procedure within 4 weeks prior to initiation of study treatment
- Inability to comply with study and follow-up procedures
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

**Concomitant 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 7 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

GDC-0032 was metabolized primarily by CYP3A4 in HLM and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low-to-moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a pharmacokinetic drug-drug interaction (DDI).

**Prohibited Therapy**

Prohibited therapy is as follows:

- **Anti-cancer therapy:** No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than letrozole permitted in this protocol) will be allowed.
- **Hormone replacement therapy**, **topical estrogens (including any intra-vaginal preparations), hormonal contraception, megestrol acetate, and selective estrogen-receptor modulators used with prophylactic intent**: If a patient is receiving these at the moment of registration, treatment should be discontinued prior to randomization.
- **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.
- **Potent CYP3A4 inhibitors:** Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole and itraconazole) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If a strong CYP3A4 inhibitor is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.
- **Potent CYP3A4 inducers:** Concomitant use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, phenobarbital) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to induce CYP3A4. If a strong CYP3A4 inducer is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.

**Length of Study**

The total duration of the study is expected to be approximately 24 months for enrollment, plus 5.5 months after last patient in.

**End of Study**

The end of the study is defined as the date when the last patient has her postsurgery visit.

**Outcome Measures**

**Co-Primary Efficacy Outcome Measures**

The co-primary efficacy outcome measures for this study are as follows:

- Tumor ORR via centrally assessed breast MRI (centrally assessed) via modified RECIST (Appendix 3) in all enrolled patients and *PIK3CA* MT patients
- pCR rate in breast and axilla (total pCR) as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system (Appendix 6) by local evaluation in all enrolled patients and *PIK3CA* MT patients

**Secondary Efficacy Outcome Measures**

The secondary efficacy outcome measures for this study are as follows:

- Tumor ORR, assessed by centrally assessed breast MRI via modified RECIST (Appendix 3) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR) by local evaluation in *PIK3CA* WT patients

The following secondary outcome measures will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of ORR, as measured by modified RECIST criteria (Appendix 3) using the following methods:
  - Breast ultrasound
  - Clinical breast exam (i.e., palpation)
  - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally derived PEPI score upon treatment with letrozole plus GDC-0032 with letrozole plus placebo
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) yoT0/is, ypNX (breast pCR)

**Safety Outcome Measures**

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0)
- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Serious adverse events
- Protocol-defined adverse events of special interest
- Clinically significant changes in vital signs and in clinical laboratory results during the adverse event reporting period (see Section 5.3.1)

**Patient-Reported Outcome Measures**

The PRO outcome measures for this study are as follows:

- HRQoL, including side-effects of therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems), and patient functioning as measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ–C30) and the modified breast cancer module QLQ–BR23

**Exploratory Outcome Measures**

The exploratory outcome measures for this study are as follows:

- ORR, pCR rate, and PEPI scores according to the decrease in Ki67 after 2 weeks of letrozole plus GDC-0032 and letrozole plus placebo.
- Expression of biomarkers before, during, and after therapy. These include, but are not limited to, the following:
  - PI3K pathway aberrations
  - Gene signatures, including intrinsic subtyping and PI3K pathway activity
  - Protein and phospho-protein markers and combinations
  - Mutations within cancer-associated genes
  - Copy number alterations in cancer-related genes
  - Plasma-based protein biomarkers
  - Circulating tumor DNA (ctDNA)
- Compare the rates of BCS and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo
- The relationship between GDC-0032 concentration and tumor response and/or drug safety response
- Letrozole concentrations with and without administration of GDC-0032
- The relationship between pharmacogenetic differences in drug metabolizing enzymes and transporters and other patient-specific covariates with PK of GDC-0032 or letrozole and/or drug response
- Changes from baseline to surgery in the apparent diffusion coefficient (ADC), a marker of tumor cellularity derived from diffusion-weighted MRI
- Concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response

**Investigational Medicinal Products**

Study treatment is neoadjuvant (pre-operative) therapy.

**Test Product**

The test product for this study is GDC-0032. Patients will receive an oral, daily dose of 4 mg (two 2-mg tablets) GDC-0032 or placebo on a schedule of 5 days on/2 days off for a maximum of 16 weeks. Patients will take GDC-0032 at the same time of day $\pm$2 hours, unless otherwise instructed. Patients will be instructed as to the number of tablets to take.

Information on the formulation, packaging, handling, and administration of GDC-0032 are provided in the GDC-0032 Investigator's Brochure.

## Non-Investigational Medicinal Products

### Letrozole

Letrozole is a marketed product that is approved in the European Union and the United States for the treatment of hormone receptor-positive breast cancer. Based upon the different mechanisms of action of GDC-0032 and the well-established safety profile of letrozole, there are no expected overlapping, significant toxicities between letrozole and GDC-0032.

Patients will receive an oral, daily dose of 2.5 mg letrozole for 16 weeks (or until time of surgery at the investigator's discretion).

## Statistical Methods

### Primary Analysis

This study is designed for testing the effect of GDC-0032 on the two co-primary endpoints in all enrolled patients and in the *PIK3CA* MT patients and plans to enroll 330 patients in total. Assuming the *PIK3CA* mutation status will not be available (unknown) for approximately 10% of the patients and the prevalence of *PIK3CA* mutant is 40%, there will be approximately 120 patients in the *PIK3CA* MT cohort.

Given that the *PIK3CA* mutation status is not a stratification factor for randomization, there might be a possible imbalance between treatment arms within the *PIK3CA* MT cohort, which may reduce the statistical power in this cohort. To ensure the study provides sufficient statistical power even when the treatment assignment is imbalanced, the sample size was calculated based on a conservative scenario by assuming that the treatment assignment imbalance in *PIK3CA* MT is 40% vs. 60%. The sample size was calculated based on a chi²-test using continuity correction (Ury and Fleiss 1980).

To control an overall two-sided, family-wise error rate under 20% *for each analysis population,* we use a two-sided significance level of 16% and 4% for the co-primary endpoints MRI ORR, and pCR, respectively.

Assuming 10% of the patients are unevaluable for the MRI ORR, approximately 300 enrolled patients and 108 patients in the *PIK3CA* MT cohort will be evaluable for analyses. This sample size allows us to detect an absolute percentage increase of 24% in MRI ORR rate in the GDC-0032 plus letrozole arm (64%) versus the letrozole-only arm (40%; Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at 80% power and 16% two-sided significance level. The minimal detectable difference for ORR is approximately 15%.

Assuming that all patients are evaluable for pCR (i.e., approximately 330 enrolled patients and 120 in the *PIK3CA* MT cohort), this sample size provides 80% power to detect an absolute percentage increase of 18% in pCR in the GDC-0032 plus letrozole arm (19%) versus the letrozole-only arm (1%, Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at the 4% two-sided significance level. The minimal detectable difference for pCR rate is approximately 13%.

If the prevalence of the *PIK3CA* mutation is lower than assumed, if there is more substantial treatment assignment imbalance in the *PIK3CA* MT cohort than assumed, or there is an increased number of unevaluable patients for the MRI ORR, the sample size may be increased to obtain the level of power at 80%, and the enrollment may be limited to patients with *PIK3CA* MT.

### Secondary Analysis

The secondary efficacy endpoints for this study are as follows:

- Tumor ORR after completion of study treatment, assessed by modified RECIST criteria by breast MRI (centrally assessed) in *PIK3CA* WT patients.
- Rate of pCR in breast and axilla (total pCR) after completion of study drug in *PIK3CA* WT patients.

These endpoint measures will be summarized by treatment arm and will be analyzed analogue to the primary efficacy endpoint.

The following secondary efficacy endpoints will be performed in all enrolled patients and separated by *PIK3CA* mutation status (centrally assessed):

- ORR using modified RECIST criteria by the following methods: by clinical breast examination, mammography and breast ultrasound
- Ki67 values at baseline, Week 3, and surgery (centrally assessed)
- Change in Ki67 from baseline to Week 3; baseline to surgery, and Week 3 to surgery (centrally assessed)
- PEPI score (centrally derived)
- Change in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluation of different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

These endpoint measures will be summarized by treatment arm and will be compared between the two treatment arms within each population based on appropriate statistical analyses: ORR will be compared using a Cochrane Mantel-Haenszel test, stratified by tumor size and nodal status; PEPI, Ki67, and tumor volume change will be compared by regression analyses, adjusted for tumor size and nodal status. All secondary endpoints will be tested at a two-sided type I error of 5%.

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

**Determination of Sample Size**

Please refer to the primary analysis in the Statistical Methods section.

**Interim Analyses**

An independent Data Monitoring Committee (iDMC) will monitor accumulating patient safety data at a minimum of once every 6 months until the last patient has completed study treatment. Additional details (e.g., DMC members, communication, affiliations) will be provided in the iDMC charter.

The iDMC will conduct interim analyses to review the unblinded safety data after the first 20 patients have either 1) finished the 30-day follow-up visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery). The iDMC will create and review unblinded, pooled summaries of the safety and available PK summaries (all interim analyses). While this review is being conducted, patient accrual into the study will continue. The Medical Monitor may also request additional safety analysis and may call for additional meetings of the iDMC to review ongoing safety data.

The iDMC will share results from interim safety analyses with the study team. The study team will share interim safety results with study investigators as needed for the conduct of the study and the safety of the patients. Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections. All available information of all enrolled patients with all available assessments at the respective timepoint will be included in the interim analyses.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ABCSG | Austrian Breast and Colorectal Cancer Study Group |
| ADC | apparent diffusion coefficient |
| AE | adverse events |
| AI | aromatase inhibitors |
| ALT | alanine transaminase |
| aPTT | activated partial thromboplastin time |
| ASCO-CAP | American Society of Clinical Oncology-College of American Pathologists |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{0-24}$ | area under the concentration–time curve from 0 to 24 hours |
| $AUC_{0-inf}$ | area under the concentration–time curve from 0 to infinity |
| BCS | breast conserving surgery |
| BIG | Breast International Group |
| BUN | blood urea nitrogen |
| CD | compact disc |
| CI | confidence interval |
| $C_{max}$ | maximum plasma concentration observed |
| $C_{min}$ | minimum concentration under steady-state conditions within a dosing interval |
| cPR | confirmed partial responses |
| CRA | clinical research associate |
| CRO | contract research organization |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating tumor DNA |
| CTNeoBC | Collaborative Trials in Neoadjuvant Breast Cancer |
| DCR | data clarification request |
| DDI | drug-drug interaction |
| $DL_{CO}$ | diffusion capacity of the lung for carbon monoxide |
| DLT | dose-limiting toxicity |
| DMP | data management plan |
| DXA | dual-energy X-ray absorptiometry |
| DVD | digital video disk |
| EC | Ethics Committee |

| Abbreviation | Definition |
|---|---|
| $EC_{50}$ | 50% effective concentration |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EGFR | epidermal growth factor receptor |
| ELISA | enzyme-linked immunosorbent assay |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ER+ | estrogen receptor-positive |
| E.U. | European Union |
| FFPE | formalin-fixed paraffin-embedded |
| FDA | Food and Drug Administration |
| FNA | fine needle aspiration |
| FSH | follicle stimulating hormone |
| GCP | good clinical practice |
| HbA1c | Glycosylated hemoglobin |
| HDL | high-density lipoprotein |
| HDPE | high-density polyethylene |
| HER2 | human epidermal growth factor receptor 2 |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HLA | human leukocyte antigen |
| HLM | human liver microsomes |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IGF-1R | insulin-like growth factor-1 receptor |
| IHC | immunohistochemistry |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (application) |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IRF | Independent Review Facility |
| ISH | in situ hybridization |

| Abbreviation | Definition |
|---|---|
| ITT | intent to treat |
| IV | intravenous |
| IxRS | interactive voice or web-based response system |
| LDL | low-density lipoprotein |
| LPLV | last patient, last visit |
| MAPK | mitogen-activated protein kinase |
| MDD | minimum detected difference |
| MP | monitoring plan |
| MRI | magnetic resonance imaging |
| MT | mutant |
| MTD | maximum tolerated dose |
| mTOR | mammalian target of rapamycin |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NGS | next generation sequencing |
| NSCLC | non – small-cell lung cancer |
| nu/nu | immunocompromised nune (mice) |
| OCT | Optimal cutting temperature |
| ORR | objective response rate |
| pAKT | phosphorylated form of AKT |
| pCR | pathologic complete response |
| PD | progressive disease |
| PEPI | preoperative endocrine prognostic index |
| PFS | progression-free survival |
| PFT | pulmonary function test |
| PI3K | phosphatidylinositol-3-kinase |
| PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha |
| PIP2 | phosphatidylinositol-4,5-bisphosphate |
| PIP3 | phosphatidylinositol 3,4,5 trisphosphate |
| PO | oral |
| PR | progesterone receptor |
| PRO | patient-reported outcome |
| PTEN | phosphatase tensin homolog |
| QD | once daily |
| QLQ-BR23 | Quality of Life Questionnaire Breast Cancer Module |
| QLQ-C30 | Quality of Life Questionnaire Core 30 |

| Abbreviation | Definition |
|---|---|
| QTcF | QT interval corrected using Fridericia's formula |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RFS | relapse-free survival |
| RPPA | reverse phase protein array |
| RT-PCR | real-time polymerase chain reaction |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SDV | source data verification |
| SLNB | sentinel lymph node biopsy |
| SOLTI | Spanish Breast Cancer Research Group |
| SOP | standard operating procedure |
| SmPC | summary of product characteristics |
| $t_{1/2}$ | terminal half-life |
| TSC1 | Tuberous Sclerosis 1 |
| TGI | tumor growth inhibition |
| ULN | upper limit of normal |
| U.S. | United States |
| WBC | white blood cell |
| WT | wildtype |

# 1. BACKGROUND

## 1.1 BACKGROUND ON THE PHOSPHATIDYLINOSITOL-3-KINASE PATHWAY

Phosphatidylinositol-3-kinase (PI3K) is a lipid kinase involved in tumor cell proliferation, survival, and migration upon activation by growth factor receptors and integrins. PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3) (Cantley 2002), a second messenger involved in the phosphorylation of AKT and associated proteins in the AKT-mammalian target of rapamycin (mTOR) pathway (Guertin and Sabatini 2007). Activating and transforming mutations, as well as amplification, in the p110$\alpha$ subunit of PI3K are commonly found in solid and hematological tumors (Li et al. 1997). In addition, the PI3K-AKT pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling, the loss of the phosphatase tensin homolog (PTEN) and Inositol Polyphosphate 4-phosphatase type II (INPP4B), or RAS mutations (Shayesteh et al. 1999; Cantley 2002; Massion et al. 2004; Wu et al. 2005).

## 1.2 BACKGROUND ON ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER

Breast cancer is the most frequently diagnosed cancer worldwide and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of total cancer deaths (Jemal et al. 2011). As a large proportion of breast cancer cases, especially in developed countries, are now diagnosed in early stages, they are amenable to cure with a stage-appropriate combination of surgery, systemic therapy (chemotherapy and/or hormonal therapy), and radiotherapy.

Estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2−) breast cancer accounts for about 60%–70% of all breast cancers. However, not all ER+ breast cancers respond optimally to endocrine therapy (Davies et al. 2011). There are several mechanisms that can lead to primary and/or secondary hormonal resistance in ER+ breast cancer: decrease of ER expression, loss of ER expression, or upregulation of growth factor signaling pathways, such as the epidermal growth factor receptor (EGFR)/HER2, the mitogen-activated protein kinase (MAPK), or the PI3K/AKT/mTOR pathways (Johnston 2009).

In the setting of ER+/HER2-negative breast cancer, the PI3K/AKT/mTOR pathway plays an important role in mediating hormonal resistance and is a viable therapeutic target to explore (Miller et al. 2010).

## 1.3 BACKGROUND ON THE PI3K/AKT/MTOR PATHWAY AND BREAST CANCER

Genes in the PI3K/AKT/mTOR signaling pathway are frequently mutated or amplified in breast cancer, especially in the ER+ subtype (Cancer Genome Atlas Network [CGAN] 2012). Molecular alterations of the PI3K/AKT/mTOR pathway include the following: (1) Mutations or amplifications in *PIK3CA*, the gene encoding the alpha catalytic subunit of PI3K (p110α) (Saal et al. 2005; Wu et al. 2005); (2) Alterations in the tumor suppressor gene *PTEN*, either by loss of protein expression (PTEN null), inactivation mutations and/or epigenetic deregulation through promoter hypermethylation (García et al. 2004); (3) PDKP1 amplification and/or overexpression (Brugge et al. 2007); (4) AKT1 somatic *gain-of*-function mutations (Stemke-Hale et al. 2008) and AKT2 amplifications (Bellacosa et al. 1995). Overall, it is estimated that up to 70% of breast cancers can have some form of molecular aberration of the PI3K/AKT/mTOR pathway (CGAN 2012).

## 1.4 BACKGROUND ON REVERSING HORMONAL RESISTANCE BY INHIBITING THE PI3K/MTOR/AKT PATHWAY

In the setting of ER+ breast cancer, *the* PI3K *signaling pathway* seems to play an important role in mediating hormonal resistance and is a viable therapeutic target. Hyperactivation of this signaling pathway was proved to promote both *de novo (primary)* and acquired *(secondary)* resistance to hormone therapy in ER+ breast cancer cell lines and xenograft models (Sabnis et al. 2007). *Simultaneous* blocking of the PI3K/AKT/mTOR pathway with everolimus*, an mTOR inhibitor,* and the ER pathway with letrozole enhances antitumor activity of either agent alone (Boulay et al. 2005). Importantly, a baseline protein signature of PI3K activation was found to be predictive of a poor prognosis after adjuvant endocrine therapy (Miller et al. 2010).

In the clinical setting, impressive results of the combination of exemestane and everolimus were reported in the BOLERO-2 trial (Baselga et al. 2009). This trial compared everolimus and exemestane with placebo and exemestane in 724 postmenopausal patients with ER+ advanced breast cancer who had experienced recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting and/or in advanced disease. Median progression-free survival (PFS) in the everolimus group was 6.9 months, as compared to 2.8 months in the placebo group. Hazard ratio (HR) for progression or death was 0.43, with a 95% confidence interval (CI) of 0.35–0.54 ($<$0.001), as per the investigator's assessment, and the magnitude of the effect was even greater as per central assessment (HR, 0.36, 95% CI, 0.27–0.47; p$<$0.001). In the open-label Phase II TAMRAD trial, patients with aromatase inhibitors (AI) resistant metastatic breast cancer received tamoxifen plus everolimus or tamoxifen alone (Bachelot et al. 2012). The 6-month clinical benefit rate was 61% (95% CI, 47%–74%) with tamoxifen plus everolimus and 42% (95% CI, 29%–56%) with tamoxifen alone. Time to progression increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus

everolimus, corresponding to a 46% reduction in risk of progression with the combination (HR, 0.54; 95% CI, 0.36–0.81). Risk of death was reduced by 55% with tamoxifen plus everolimus versus tamoxifen alone (HR, 0.45; 95% CI, 0.24–0.81).

In the neoadjuvant setting, combination of letrozole and everolimus also resulted in improved responses over letrozole alone in patients with ER+ breast cancer (Baselga et al. 2009). In this study, 270 postmenopausal patients with operable ER+ breast cancer were randomly assigned to receive 4 months of neoadjuvant treatment with letrozole and either everolimus or placebo. The primary endpoint of the trial, clinical response by palpation, was higher in the everolimus arm than in the control arm (68.1% vs. 59.1%, $p = 0.062$), a statistically significant result (one-sided, $\alpha = 0.1$ level).

An important finding in trials with mTOR-targeting drugs like everolimus is that they produce a pharmacodynamic paradox: while inhibiting mTOR, they lead to an upregulation of the phosphorylated form of AKT (pAKT), resulting in feedback PI3K/AKT/mTOR pathway activation (Tabernero et al. 2009). This finding suggests that alternative pharmacologic strategies to effectively shut down the pathway upstream of AKT should be pursued. One of these strategies is inhibiting the PI3K/AKT/mTOR pathway at the level of PI3K.

## 1.5 BACKGROUND ON NEOADJUVANT THERAPY IN 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 and Smith 2003; Scholl et al. 1994; Semiglazov et al. 2004; Fisher et al. 2012; Wolff and Davidson 2000). The randomized studies evaluating neoadjuvant therapy as well as meta-analyses of these studies have shown that neoadjuvant therapy can improve breast conservation rates, decreasing the number of women obligated to undergo mastectomy (Mieog et al. 2007; Fisher et al. 2012). 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 distant disease recurrence based upon the timing of the systemic therapy (Mauri et al. 2005). The concept of neoadjuvant therapy is now well established and a standard treatment option for patients with early breast cancer. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis was recently conducted evaluating over 12,000 patients treated with neoadjuvant chemotherapy as part of clinical trials (Cortazar et al. 2014). The results of this meta-analysis confirmed an association of pCR with favorable long-term outcomes in high-risk populations (i.e., HER2-positive, high-grade hormone receptor positive and triple negative subtypes), although the magnitude of pCR improvement predictive of the long-term survival benefits could not be determined. In September 2013, the Food and Drug Administration (FDA) granted accelerated approval of *pertuzumab* (Perjeta®) as part of a complete treatment

regimen for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer in the neoadjuvant setting.

## 1.6 BACKGROUND ON GDC-0032

GDC-0032 (also known as taselisib) is a potent selective inhibitor of Class I PI3K alpha, delta, and gamma isoforms, with 30-fold less potent inhibition of the beta isoform that is being developed as a therapy for human cancers. Nonclinical studies with GDC-0032 demonstrate that GDC-0032 inhibits proliferation of p110$\alpha$-mutant breast cell lines, inhibits tumor growth in human breast xenograft models harboring *PIK3CA* mutations, and results in a substantial reduction of PI3K pathway markers, including pAkt, pPRAS40, and pS6.

GDC-0032 has demonstrated activity in *preclinical* models of *PIK3CA*-mutant breast tumors in vivo as a single agent and in combination with standard of care (e.g., paclitaxel or docetaxel) or endocrine therapies (e.g., letrozole or fulvestrant). GDC-0032 has a favorable in vitro and nonclinical in vivo absorption, distribution, metabolism, and elimination profile that has characteristics consistent with a compound that can be delivered orally to achieve clinical exposure similar to the nonclinical efficacy findings described herein. Additional studies, including 16-week toxicity studies in rats and dogs, phototoxicity studies, and an embryo-fetal development study, support the Phase II neoadjuvant trial with GDC-0032 in combination with endocrine therapy.

In vitro, single-agent GDC-0032 potency is also observed in cell lines that do not harbor *PIK3CA* mutations (see Figure 1). In in vitro combination studies, the aromatase-expressing breast cancer cell line (MCF7X2.3.ARO) showed positive combination effects between GDC-0032 and endocrine therapies (see Figure 2). In this cell line, GDC-0032 alone caused growth inhibition (50% effective concentration [$EC_{50}$] = 95 nM). Effects on growth were also observed with letrozole and fulvestrant. Combined treatment of cells with GDC-0032 and letrozole caused dose-dependent inhibition of cell viability at lower concentrations of either GDC-0032 or letrozole resulting in enhanced activity for the combination. In addition, combination activity was demonstrated in the *PIK3CA* wild-type (WT) cell line ZR75-1 when GDC-0032 was added to either fulvestrant or tamoxifen endocrine therapies (combination with letrozole not available in this cell line). However, in vivo data in a *PIK3CA* WT model are not available because these cell lines do not grow as xenografts.

**Figure 1 GDC-0032 Potency in Non-*PIK3CA* Mutant Breast Cancer Cell Lines**

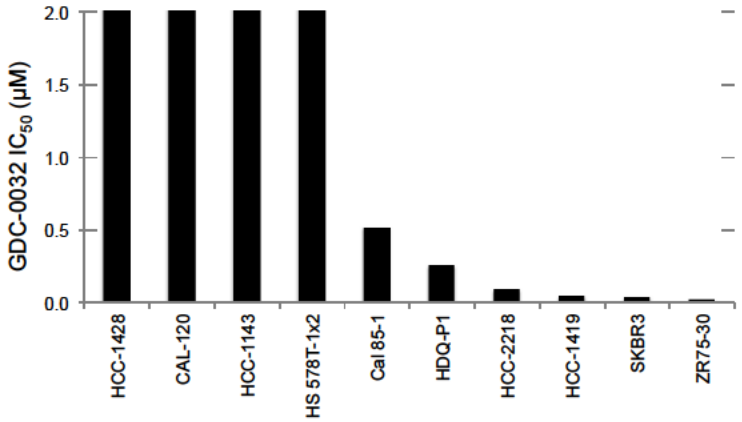
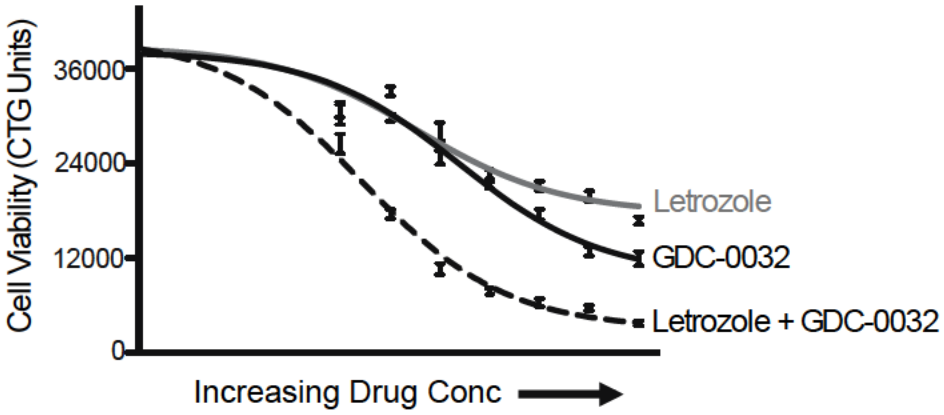



**Figure 2 Combination Effects between Letrozole and GDC-0032 in the Aromatase-Expressing MCF7.2x3 Breast Cancer Cell Line**



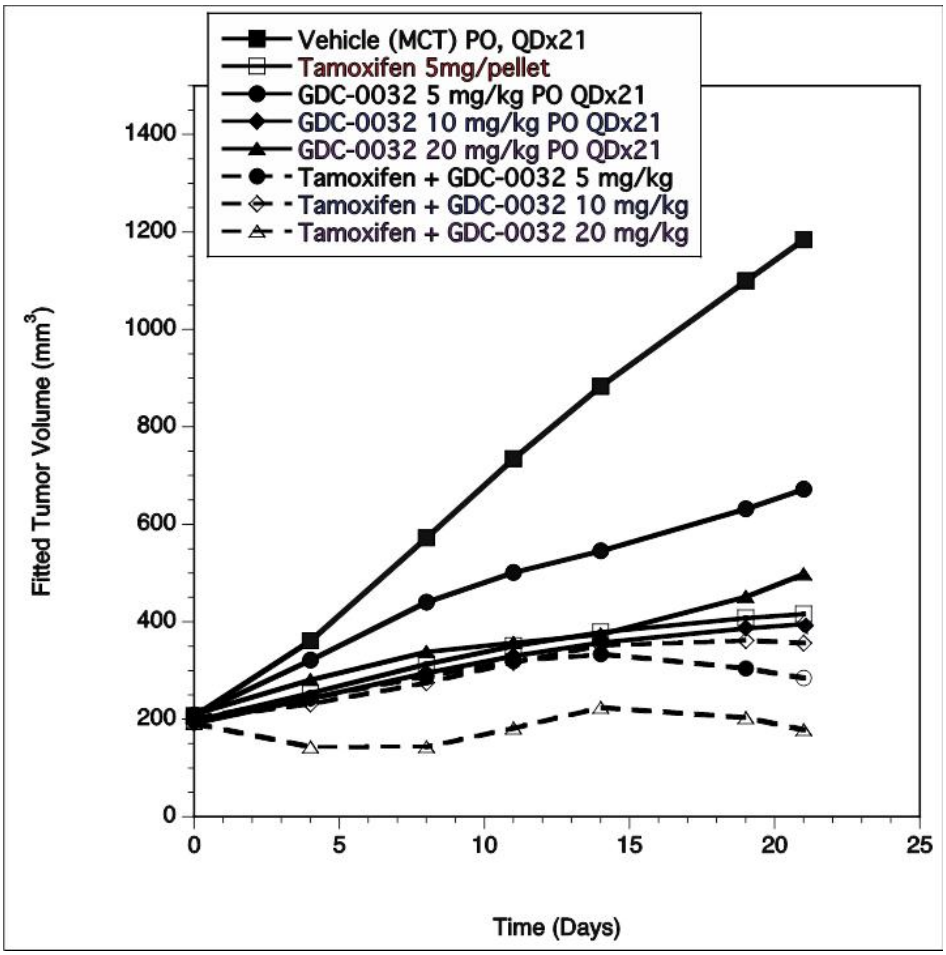

Conc = concentration.

MCF7X2.3.ARO (aromatase-expressing MCF7 cells) are sensitive to GDC-0032 in combination with endocrine therapies. Effects on viability are determined after 96 hours in culture.

Enhanced efficacy was demonstrated in combination with tamoxifen, another endocrine therapy used in the treatment of hormone receptor-positive breast cancer. In this human MCF7-neo/HER2 (*PIK3CA* mutant [MT]) breast cancer xenograft model in immunocompromised nude (nu/nu) mice, administration of GDC-0032 at all doses tested (5, 10, or 20 mg/kg) in combination with tamoxifen (5-mg/pellet) resulted in greater efficacy (shown as a percentage of tumor growth inhibition [TGI]: 82% TGI, 80% TGI, and 102% TGI, respectively) compared with tamoxifen alone (73% TGI) or GDC-0032 as a single agent (71% TGI at 20 mg/kg) (see Figure 3). All combinations were well

tolerated with no increase in mortality and no greater body weight loss than single agents alone.

**Figure 3 Efficacy of Tamoxifen in Combination with GDC-0032 in MCF7-Neo/Her2 Estrogen Receptor-Positive Mouse Xenografts**




QD = once daily; PO = oral gavage.

Vehicle was MCT (0.5% methycellulose/0.2% Tween-80).

Tamoxifen pellets (5 mg/pellet, 60-day release) were implanted on Day 0 of dosing (8 days post tumor implantation). Tumor volumes after QD oral administration of GDC-0032 for 21 days are depicted by dose group.

Please refer to the GDC-0032 Investigator's Brochure for additional nonclinical data for GDC-0032 supporting this clinical trial.

### 1.6.1 Toxicology

Please refer to the GDC-0032 Investigator's Brochure for details on the toxicology program to support this clinical trial.

## 1.7 SUMMARY OF CLINICAL DATA FOR GDC-0032

### 1.7.1 Clinical Safety Data with GDC-0032

As of 5 July 2013, a total of 144 patients have been treated with GDC-0032 capsules, in the Phase I/II PMT4979g study, either as single agent (n = 90, 63%) or in combination with endocrine therapy (n = 54, 37%).

As of 5 July 2013, enrollment into the dose-escalation stage of Study PMT4979g had been completed with 34 patients enrolled at GDC-0032 doses ranging from 3–16 mg daily. GDC-0032 was well tolerated in the first three cohorts (3, 5, and 8 mg), with no patients experiencing a dose-limiting toxicity (DLT). At the 16-mg dose level, 2 of the 11 safety-evaluable patients experienced a DLT (Grade 4 hyperglycemia and Grade 3 fatigue). At the 12-mg dose level, 1 of the 10 safety-evaluable patients experienced a DLT of Grade 3 acute renal failure. Although the single-agent GDC-0032 maximum tolerated dose (MTD) was not exceeded at the 16-mg dose level, the recommended GDC-0032 dose and schedule for the single-agent expansion cohorts is 9 mg daily on the basis of long-term safety data through multiple treatment cycles. As of the cutoff date, a total of 53 patients had been enrolled in the 9-mg daily dosing expansion cohorts.

As of 5 July 2013, adverse events of any grade that occurred in ≥ 10% of the 87 patients treated with daily single-agent GDC-0032 capsules and were investigator-assessed as related to GDC-0032 were as follows: diarrhea (47%), hyperglycemia (38%), nausea (36%), fatigue (35%), decreased appetite (31%), rash (25%), stomatitis (13%), vomiting (13%), and mucosal inflammation (12%). Grade 3 and 4 adverse events assessed by the investigator as GDC-0032 related included hyperglycemia (12%), colitis (6%), rash (5%), diarrhea (3%), fatigue (3%), pneumonitis (3%), pruritus (2%), stomatitis (2%), increased alanine aminotransferase levels (1%), anemia (1%), increase in blood creatinine (1%), exfoliative rash (1%), hypokalemia (1%), hypophosphatemia (1%), lung infection (1%), pneumonia (1%), erythematous rash (1%), generalized rash (1%), maculopapular rash (1%) and skin exfoliation (1%), and acute renal failure (1%).

As of 5 July 2013, a total of 27 patients have been enrolled in the expansion cohort of GDC-0032 at dose levels of 6 and 9 mg daily (19 patients at 6 mg, and 8 patients at 9 mg) daily in combination with letrozole (Cohort E). No DLTs were observed at either dose level. Adverse events of any grade and assessed by the investigator as drug related that occurred in ≥ 10% of the 27 safety-evaluable patients assessed as related to GDC-0032 were diarrhea (67%), fatigue (30%), nausea (30%), rash (30%), decreased appetite (26%), hyperglycemia (26%), stomatitis (26%), dysgeusia (22%), mucosal inflammation (19%), asthenia (15%), pruritis (15%), vomiting (15%), and dry mouth (11%). Grade 3 and 4 adverse events assessed by the investigator as GDC-0032 related include diarrhea (11%), mucosal inflammation (7%), increased amylase (4%), hyperglycemia (4%), increased AST (4%), stomatitis (3.7%), increased blood alkaline phosphate (4%), fatigue (4%), increased gamma-glutamyltransferase in the blood (4%), hypokalemia (4%), increased lipase in the blood, (4%), and papilloedema (4%).

As of 5 July 2013, a total of 27 patients have been enrolled in the expansion cohort of GDC-0032 at dose levels of 6 and 9 mg daily (21 patients at 6 mg and 6 patients at 9 mg) in combination with fulvestrant (Cohort F). No DLTs were observed at either dose level. One patient has been enrolled in the Phase II part of the study with 6 mg GDC-0032 in combination with fulvestrant. Adverse events assessed by the investigator as GDC-0032 related and of any grade that occurred in ≥ 10% of the 27 patients and were assessed as related to GDC-0032 were diarrhea (48%), hyperglycemia (33%), nausea (33%), decreased appetite (26%), fatigue (26%), rash (26%), stomatitis (22%), asthenia (19%), muscle spasms (15%), vomiting (15%), dysgeusia (11%), gastroesophageal reflux disease (11%) and mucosal inflammation (11%). Grade 3 and 4 adverse events assessed by the investigator as related to GDC-0032 included hyperglycemia (15%), diarrhea (7%), dyspnea (4%), flank pain (4%), hyponatremia (4%), neutropenia (4%), rash (4%) and vomiting (4%).

Please refer to the GDC-0032 Investigator's Brochure for additional information.

#### 1.7.1.1 Preliminary Pharmacokinetics

Pharmacokinetic (PK) data are available from 34 patients treated with GDC-0032 at 3, 5, 8, 12, and 16 mg in the ongoing Phase I/II clinical trial (Study PMT4979g). The cohort mean apparent clearance and the terminal half-life ($t_{1/2}$) following a single, oral dose of GDC-0032 had a range of 4.77–9.17 L/hour and 36.7–43.8 hours, respectively. Following daily oral dosing for 8 days, there was a 2- to 4-fold accumulation of GDC-0032. The pharmacokinetics of GDC-0032 appears to be dose linear and time-independent. Preliminary PK data from Cohort E suggest there is no drug-drug interaction (DDI) between letrozole plus GDC-0032. Mean plasma exposure of letrozole when given in combination with GDC-0032 (maximum concentration observed [$C_{max}$] = 0.407 μM and area under the concentration–time curve from 0 to 24 hours [$AUC_{0-24}$] = 8.01 μM*hr) was comparable with the historical single-agent exposure ($C_{max}$ = 0.495 μM and $AUC_{0-24}$ = 10.1 μM*hr) (Awada et al. 2008). Similarly, plasma concentrations of GDC-0032, when given in combination with letrozole, were within the range predicted by the population PK model. Therefore, letrozole plus GDC-0032 can be co-administered without the risk of a DDI.

GDC-0032 was metabolized primarily by CYP3A4 in human liver microsomes (HLMs) and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low to moderate potential to induce CYP3A4, preliminary data from the Phase I/II study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a PK DDI.

Preliminary data from a healthy volunteer study showed that the 3-mg GDC-0032 tablet produces an estimated geometric mean ratio (90% CI) of 196% (177.1–217.0) for $C_{max}$

and 152.2% (141.9–163.2) for AUC time 0 to infinity ($AUC_{0\text{-}inf}$) when compared with the 3-mg Phase I capsule. For this reason, a new 2-mg tablet has been formulated to deliver GDC-0032 exposure similar to the 3-mg capsule formulation.

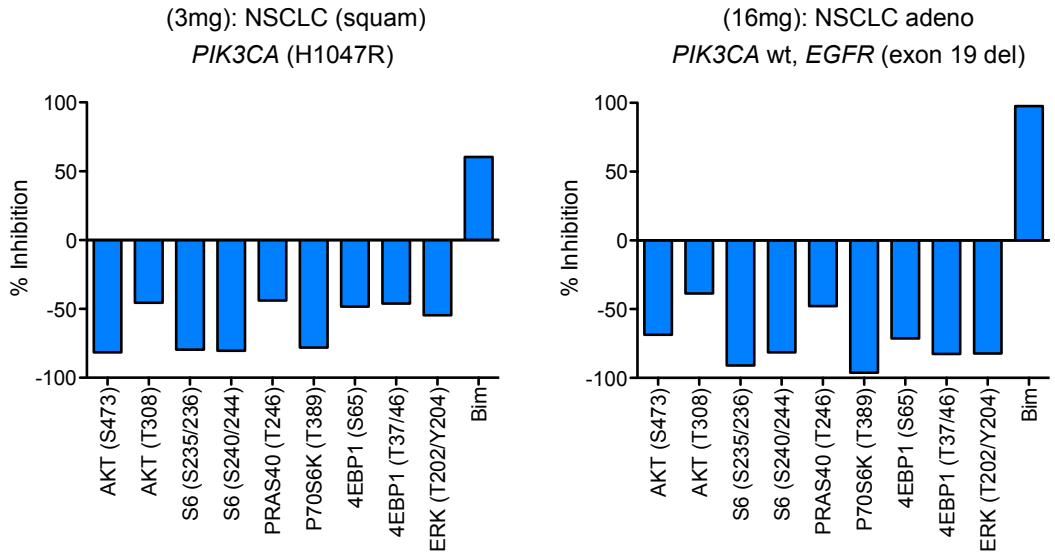
The drug exposure (AUC) for GDC-0032 in a healthy volunteer study was minimally affected by the consumption of a high-fat meal. Therefore, GDC-0032 may be taken without regard to the timing of the administration of food.

For additional details, refer to the GDC-0032 Investigator's Brochure.

#### 1.7.1.2 Preliminary Pharmacodynamics

Paired tumor biopsies were obtained from both *PIK3CA* MT and *PIK3CA* WT non-small cell lung cancer (NSCLC) patients treated at either the 3-mg or 16-mg GDC-0032 dose level, respectively, at screening (pretreatment biopsy) and during Cycle 1 in Study PMT4979g (on-treatment biopsy). Inhibition of PI3K pathway markers, including decreases of >60% in pAKT and pS6 (compared with baseline), were demonstrated in these patients' paired tumor biopsies (see Figure 4).

**Figure 4 Decrease in PI3K Pathway Activation in Tumor Biopsies Observed upon GDC-0032 Treatment in Both *PIK3CA* MT and WT Tumors**




MT = mutant; NSCLC = non – small-cell lung cancer; WT = wild type.

As of 5 July 2013, metabolic partial responses via FDG-PET (≥20% decrease in maximum standardized uptake value) were observed in 23 out of 38 patients assessed (61%) and included patients from the lowest dose tested (3 mg). Thirteen of these 23 were patients with breast cancer. Of the 13 response-evaluable patients treated with GDC-0032 plus letrozole, 10 patients (77%) had a partial metabolic response. Of the

15 response-evaluable patients treated with GDC-0032 plus fulvestrant, 11 (73%) had a partial metabolic response.

For additional details, refer to the GDC-0032 Investigator's Brochure.

## 1.8 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Cancer is one of the leading causes of death worldwide, with solid tumors accounting for the majority of these deaths. An estimated 1.38 million women across the world were diagnosed with breast cancer in 2008, accounting for 23% of all cancers diagnosed in women. Breast cancer is the most common cause of death from cancer in women worldwide, estimated to be responsible for almost 460,000 deaths in 2008 (Ferlay et al. 2010).

A neoadjuvant study in a similar patient population with the combination of letrozole and the mTOR inhibitor everolimus has already been completed (Baselga et al. 2009). Please refer to Sections 1.4, 1.5, and 3.3 for further rationale supporting the proposed trial design of combining GDC-0032 with letrozole in the neoadjuvant setting for this patient population. In postmenopausal women with hormone receptor-positive metastatic breast cancer, it is hypothesized that the combination of decreasing estrogen levels with letrozole and inhibition of the PI3K pathway with GDC-0032 may have improved anti-tumor activity as compared to endocrine therapy alone. This is supported by the nonclinical and clinical data outlined below.

GDC-0032 is a potent, selective small molecule inhibitor of Class 1 PI3K that is being developed by Roche/Genentech as an anti-cancer therapeutic agent. Activating and transforming mutations in the p110 alpha subunit of PI3K are commonly found in tumors. GDC-0032 has been shown to be a potent inhibitor of growth in various human cancer cell lines, and especially in nonclinical models of *PIK3CA* MT tumors. In addition, combination activity was demonstrated in the *PIK3CA* WT cell line ZR75-1 when GDC-0032 was added to either fulvestrant or tamoxifen endocrine therapies (combination with letrozole not available in this cell line).

GDC-0032 has also shown additive efficacy in combination with endocrine therapy in a hormone receptor-positive breast cancer xenograft model as outlined in Section 1.6. Nonclinical data support the investigation of GDC-0032 as a single-agent in solid tumors and in combination with endocrine therapy in patients with hormone receptor-positive breast cancer.

Available clinical data with single-agent GDC-0032 suggest that GDC-0032 has dose-linear pharmacokinetics with a half-life of approximately 37–44 hours. Pharmacodynamic markers of PI3K pathway inhibition upon treatment with GDC-0032 have been observed. These include decreases in phospho-S6 in platelet-rich plasma and decreases in F-flurodeoxyglucose-positron emission tomography uptake. Available clinical data also include multiple confirmed partial responses in patients treated with

GDC-0032. These include a patient with *PIK3CA* MT lung adenocarcinoma treated at the 3-mg daily dose and another patient with *PIK3CA* MT, hormone receptor-positive, HER2-positive metastatic breast cancer treated at the 5-mg daily dose. In addition, a patient with *PIK3CA* WT lung cancer treated at the 3-mg daily dose has had prolonged stable disease and remained on study for over 11 months. These data show that single-agent GDC-0032 doses below 6 mg have been shown to have anti-tumor activity. These aggregate data support the use of 6 mg in combination with letrozole.

Letrozole is a marketed product that is approved in the European Union (E.U.) and the United States (U.S.) for the treatment of hormone receptor-positive breast cancer. Based upon the different mechanisms of action of GDC-0032 and the well-established safety profile of letrozole, there are no expected overlapping, significant toxicities between letrozole and GDC-0032.

As of 5 July 2013, efficacy data are available for 24 patients treated with GDC-0032 capsules in combination with letrozole; 3 patients (12.5%) had a partial response as best overall response, 2 of which were confirmed partial responses (cPRs) (1 cPR at 6 mg; 1 cPR at 9 mg). Of the 25 efficacy-evaluable patients treated with GDC-0032 in combination with fulvestrant, 7 patients (28%) had a partial response as best overall response, of which 3 were cPRs (1 cPR at 6 mg; 1 partial response at 9 mg). cPRs have been observed in both *PIK3CA* mutant and *PIK3CA* WT patients with breast cancer. Maintenance of cPR has been observed in a patient who had a dose reduction from 6 mg to 3 mg for an adverse event. In addition, no additional safety concerns have been observed with GDC-0032 in combination with letrozole in the ongoing Phase I study compared to GDC-0032 given as single agent.

A number of clinically appropriate strategies to minimize risk to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, protocol design, and management guidelines. These will also be clearly highlighted and discussed in detail at investigator meetings and site visits. In addition, please refer to the GDC-0032 Investigator's Brochure for details regarding potential risks, associated precautions, and other relevant nonclinical and clinical safety information.

Due to the need to develop improved therapies to reverse or delay resistance to current endocrine therapy in HER2-negative, hormone receptor-positive breast cancer and on the basis of the clinical and nonclinical data available for GDC-0032, Genentech/Roche feels that the risk-benefit profile of GDC-0032 in combination with letrozole in postmenopausal patients with HER2-negative, hormone receptor-positive early stage breast cancer is favorable for proceeding with the proposed randomized Phase II clinical trial.

# 2. OBJECTIVES

## 2.1 EFFICACY OBJECTIVES

The primary objective of this study is to evaluate the efficacy of letrozole plus GDC-0032 versus letrozole plus placebo in women with ER+/HER2− early stage breast cancer, as measured by the following co-primary endpoints:

- Tumor overall objective response rate (ORR) by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in all enrolled patients and *PIK3CA* MT patients
- pCR rate in breast and axilla (ypT0/Tis ypN0) by local evaluation in all enrolled patients and *PIK3CA* MT patients

The secondary efficacy objectives of this study are the following:

- Tumor ORR, assessed by centrally assessed breast MRI via RECIST in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR ypT0/Tis ypN0) by local evaluation in *PIK3CA* WT patients

The following secondary objectives will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of locally assessed ORR as measured by modified RECIST criteria (Appendix 3) using the following methods:
    - Breast ultrasound
    - Clinical breast exam (i.e., palpation)
    - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally derived, preoperative endocrine prognostic index (PEPI) score upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo.
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment.
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

## 2.2 SAFETY OBJECTIVES

The safety objective for this study is as follows:

- Evaluate the safety of letrozole plus GDC-0032 versus letrozole plus placebo

## 2.3 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for this study are as follows:

- Evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23)

## 2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess whether biomarkers from tumor tissue or blood, including but not limited to somatic cancer associated mutations, PTEN expression, pro-survival pathways (such as PI3K/AKT, MAPK etc.), apoptotic markers, hormone receptor expression levels, and levels of RNA and DNA expression are predictive of response
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to anti-tumor activity
- To assess concordance and percentage of *PIK3CA* mutation status from baseline biopsy and surgical specimen
- To assess emergence of resistance alleles from tumor tissue or blood
- To assess concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response
- To assess the pharmacokinetics and possible drug interaction between letrozole and GDC-0032 upon concomitant administration
- To assess the correlation of GDC-0032 drug levels and GDC-0032 related response (efficacy or adverse events [e.g., colitis, rash])
- To assess the influence of pharmacogenetic polymorphisms on GDC-0032 and/or letrozole on pharmacokinetics and response (either efficacy and/or adverse events)
- Compare the rates of breast-conserving surgery (BCS) and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo.

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF STUDY

This is a two-arm, randomized, double-blind, multicenter, pre-operative study to evaluate the effect of combining letrozole and GDC-0032 versus letrozole and placebo in postmenopausal women with ER+/HER2- untreated, Stage I–III operable breast cancer whose primary tumors are $\geq$ 2 cm. Patients with cT4 or cN3 tumors are not eligible.

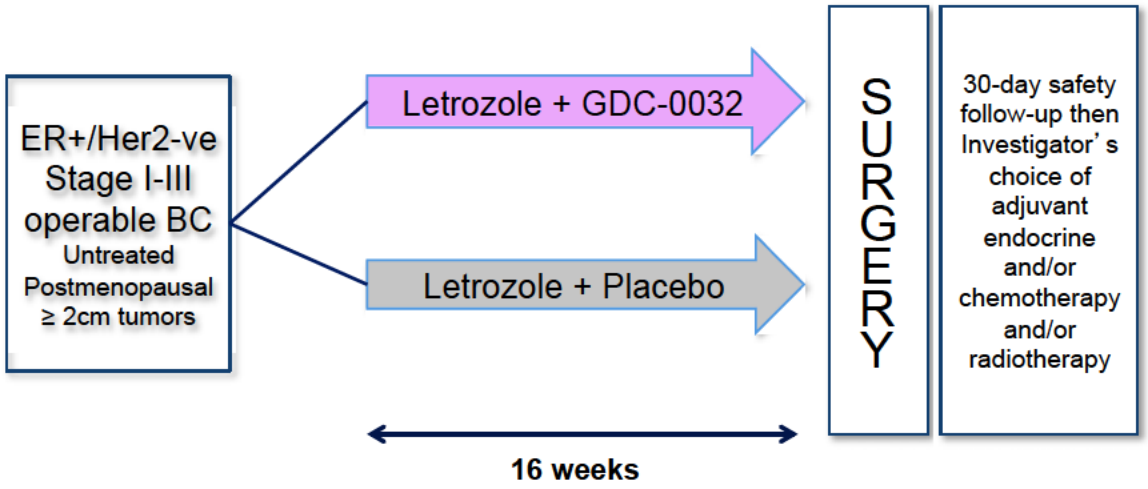
Standard of care assessments/procedures (e.g., bilateral mammogram) performed within 28 days of Day 1 dosing do not need to be repeated for screening purposes.

All patients will undergo pretreatment tumor tissue acquisition (snap-frozen [optimal cutting temperature; OCT] and formalin-fixed paraffin-embedded cores [FFPE]). Two pretreatment FFPE core biopsies and one freshly frozen core biopsy must be obtained for all patients prior to beginning study drug treatment. Tumor tissue from prior diagnostic FFPE core biopsies may be used for enrollment eligibility purposes. For the purpose of enrollment, ER, progesterone receptor (PR), and HER2 will be locally determined prior to beginning of study treatment. Remaining tissue will be retained for future translational studies. Presurgical sentinel lymph node biopsy (SLNB) is not allowed.

Patients will be randomized into one of the two treatment arms with a 1:1 randomization ratio. Letrozole at 2.5 mg will be dosed once daily plus either GDC-0032 at 4 mg (two 2-mg tablets) or placebo on a 5–days-on/2–days-off schedule for a total of 16 weeks (see Figure 5). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

**Figure 5 Study Schema**

Letrozole 2.5 mg QD + GDC-0032 4 mg or placebo QD on a 5–days-on/2–days-off schedule




| | Pretreatment | Day 15 (Week 3) | Week 9 | Week 16 | Surgery (Week 17-18) |
|---|---|---|---|---|---|
| Tumor tissue | ● | ● | | | ● |
| MRI | ● | | ● | ● | |
| Breast U/S | ● | | ● | ● | |
| Mammogram | ● | | | ● | |

BC = breast cancer; ER + = estrogen receptor positive; HER2 = Human Epidermal Growth Factor Receptor 2; MRI = magnetic resonance imaging; QD = once daily; U/S = ultrasound.

After confirmation of all the eligibility criteria, patients will be randomized to one of the treatment arms. A second biopsy will be performed on Day 15 (Week 3) for biomarker analyses. Biopsies should be performed at least 2 hours after GDC-0032 dose administration.

Randomization will be stratified according to 2 factors:

1. Tumor size (T1-T2 vs. T3)
2. Nodal status (cytologically positive vs. radiologically or cytologically negative)

The study will enroll approximately 330 patients at approximately 110 global sites.

At Weeks 1, 5, 9, 13, and 16 the primary breast tumor and axillary lymph nodes will be assessed by clinical breast examination (palpation and caliper measurement).

Suspicion of progression based on clinical exam at any time should be further evaluated (see Figure 6).

*In addition to the safety assessments conducted at the scheduled follow-up visits, patients will be contacted by telephone for a general assessment of adverse events at Weeks 7 and 11.*

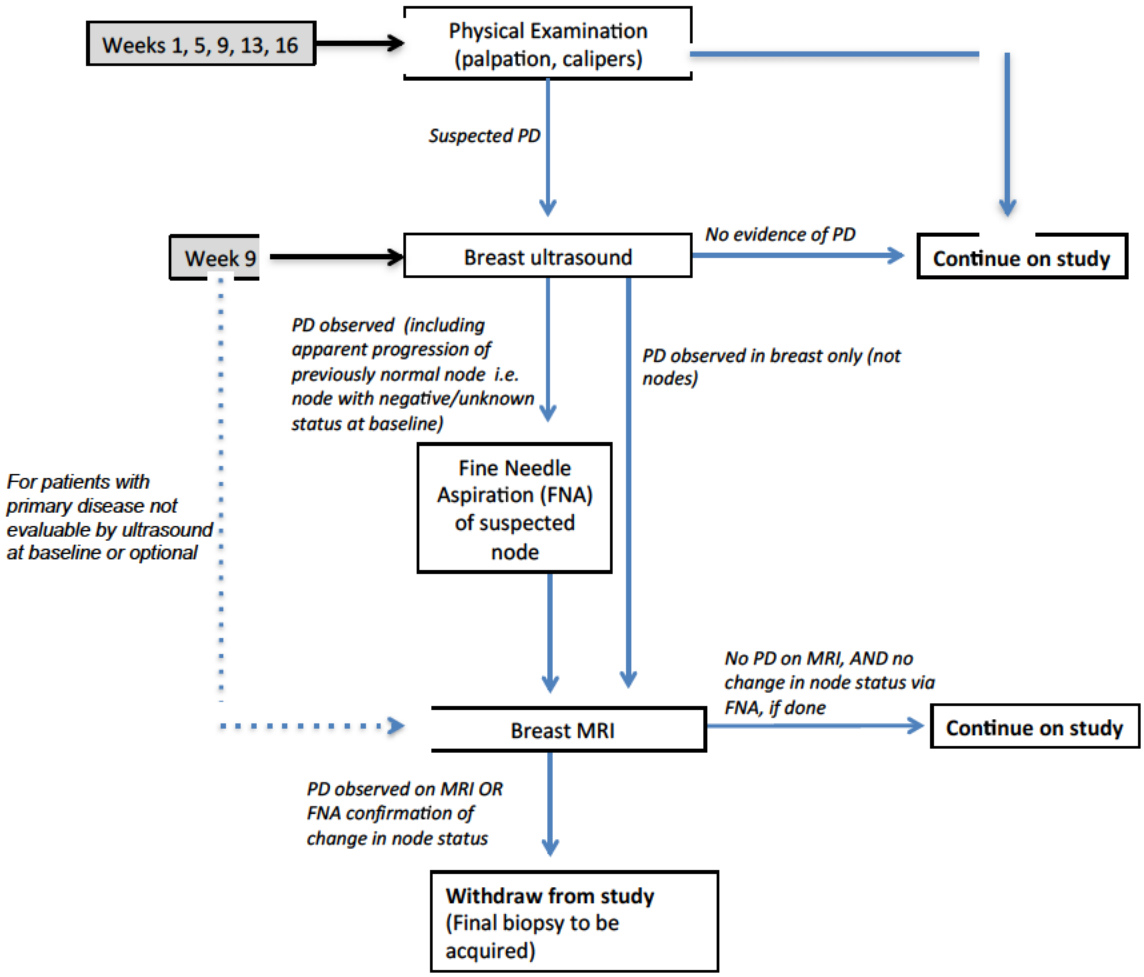
At Week 9, a breast ultrasound will be performed to ensure that there is no progressive disease and for the purpose of surgery planning. Suspicion of progressive disease on breast ultrasound should be confirmed by investigator-assessed breast MRI. Patients with primary disease not evaluable by ultrasound at baseline should be assessed by MRI at Week 9. Suspected progression in nodes should also be confirmed by fine needle aspiration (FNA) if these nodes had not been previously shown to be cytologically positive for cancer. Patients with progressive disease (as defined by modified RECIST, Appendix 3) can either proceed directly to surgery or be taken off of the study, according to the investigator's decision. If the patient goes off-study, every reasonable effort should be made to obtain a new biopsy sample prior to beginning another systemic treatment.

From Week 13, the patient will visit with the surgeon. The purpose of this visit is two-fold: tentative planning of the type of breast surgery to be performed (breast conservative vs. mastectomy) and scheduling the date for definitive surgery.

During Week 16, breast MRI will be done for the purpose of primary endpoint analysis. Clinical breast examination, breast ultrasound, and mammography will also be conducted prior to surgery for the purpose of the secondary endpoint analysis.

Blood sample*s* for exploratory endpoint analysis will be collected on Day 1 prior to dosing, at Week 9, prior to surgery *(Week 16 visit,) and at the 4-weeks postsurgical follow-up visit*.

**Figure 6 Schematic Representing Confirmation of Progression**




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

### 3.1.1 Surgery

Surgery will take place after at least 16 weeks of treatment, during Weeks 17–18. Surgery should be performed within 4 days after the last dose of GDC-0032, if possible, to best observe pharmacodynamic knockdown with GDC-0032 in the surgical specimen. Surgery may be delayed due to toxicity or other safety issues, upon discussion with the Medical Monitor (see Section 5.4.1) or recommendations from the independent Data Monitoring Committee (iDMC; see below). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

Breast and axillary surgery will follow local practice. However, presurgical SLNB is not allowed. Information on the type of surgery will be collected and recorded. Surgery specimens will be collected for histological examination to assess for pCR and for other endpoint analyses.

Following surgery, follow-up will proceed according to local standards of care. Adjuvant endocrine therapy and/or chemotherapy will be delivered as per the investigator's choice. Postoperative radiotherapy is required if BCS is performed. In the event of mastectomy, radiotherapy is to be administered according to local guidelines.

A postsurgery visit will be performed 4 weeks (+1 week) after surgery, and will mark the end of the study. Assessment of adverse events and general safety will be collected at this visit and the plan for future treatment will be recorded.

The patient should be evaluated at baseline and after Week 13 of treatment for planning the surgical procedure (BCS or mastectomy), and both the planned and actual surgical treatment should be documented in the electronic Case Report Form (eCRF).

The co-primary efficacy endpoint, pCR (pCR–ypT0/is, ypN0) will be established via a local review following completion of neoadjuvant therapy and surgery.

Please refer to the pathology manual for further guidance of evaluation for pCR and directions for sending a copy of the pathology report.

A schedule of assessments is provided in Appendix 1.

An Independent Review Facility (IRF) will be used to determine the tumor ORR via MRI. IRF procedures are detailed in the IRF charter.

### 3.1.2 Independent Data Monitoring Committee

An iDMC will monitor accumulating patient safety data at a minimum of once every 6 months until the last patient has completed study treatment. Additional details (e.g., iDMC members, communication, affiliations) will be provided in the iDMC charter.

The iDMC will review the unblinded safety data after the first 20 patients have either 1) finished the 30-day follow-up visit after the surgery, or 2) been in the study for 20 weeks after the randomization date (for those who do not receive the surgery), whichever occurs first. While this review is being conducted, patient accrual into the study will continue. The Medical Monitor may also request additional safety analysis and may call for additional meetings of the iDMC to review ongoing safety data.

## 3.2 END OF STUDY

The end of the study is defined as the date when the last patient has her postsurgery visit. The total duration of the study is expected to be approximately 24 months for enrollment, plus 5.5 months after last patient in.

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Conducting the Study in the Neoadjuvant Setting

Breast cancer is a heterogeneous disease, and not every breast tumor responds equally to a specific agent. Studies based on global gene expression analyses have provided additional insights into this complex scenario. Over the past 10 years, four major classes of breast cancer (Luminal A, Luminal B, HER2-enriched, and basal-like) have been identified and intensively studied (Perou et al. 2000; Sørlie et al. 2001). Known as the intrinsic subtypes of breast cancer, these groups of tumors have revealed critical differences in incidence, survival, and response to treatment *(Sotiriou et al. 2003)*. As genomic studies evolve, further sub-classifications of breast tumors are expected to emerge. Thus, a major challenge in breast cancer management is how to prospectively select patients who will derive the maximum benefit from a given drug regimen and minimizing unnecessary toxicities for patients with non-responsive disease.

Neoadjuvant therapy, a systemic therapy administered prior to breast cancer surgery, is now widely used in the treatment of patients with early breast cancer. 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, especially those with larger tumors. The tumor may shrink prior to surgery, thus increasing the rate of BCS (Coudert et al. 2006), and since the response to therapy can be monitored, the patient might be also spared further treatment with inactive medications.

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 prespecified in order to monitor treatment response at a biological level. Finally, the surgical specimen, if pCR is not reached, can be utilized as well. 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 (von Minckwitz and Fontanella 2013; Cortazar et al. 2012).

### 3.3.2 Rationale for Patient Population

Postmenopausal patients with HER2-negative, ER+, early stage breast cancer will be enrolled in this study. This patient population is usually treated with a combination of surgery, anti-hormonal therapy, and/or chemotherapy, according to staging and biological features.

Recently, everolimus was approved by the FDA and European Medicines Agency in combination with exemestane for the treatment of advanced or metastatic breast cancer in patients after recurrence or progression following treatment with nonsteroidal aromatase inhibitors (AIs). In the neoadjuvant setting, a combination of letrozole and

everolimus resulted in improved responses over letrozole alone in patients with ER+ breast cancer (Baselga et al. 2009).

Important findings in trials with drugs targeting mTOR, like everolimus, confirm a previously identified pharmacodynamic paradox: while inhibiting mTOR, they lead to an upregulation of the pAKT, resulting in feedback PI3K/AKT/mTOR pathway activation through an insulin-like growth factor-1 receptor (IGF-1R) mediated feedback loop (Tabernero et al. 2009). This finding suggests that alternative pharmacologic strategies to shut down the pathway upstream of AKT should be pursued. One of these strategies is to inhibit the PI3K/AKT/mTOR pathway at the PI3K level. PI3K-inhibitors are central regulators of the mTOR signaling pathway, and nonclinical findings show that PI3K-inhibitors and dual PI3K-mTOR inhibitors induce a greater amount of apoptosis than everolimus in estrogen-deprived in vitro models (Sanchez et al. 2011); therefore, it is hypothesized that PI3K-inhibitors may be active and demonstrate greater anti-tumor activity as compared to AIs alone in the neoadjuvant setting.

### 3.3.3 Rationale for Control Group

AIs have been found to be more effective than tamoxifen as a neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer.

Several trials have assessed the efficacy and safety of neoadjuvant endocrine therapy using AIs in patients with postmenopausal breast cancer (Eiermann et al. 2001; Smith et al. 2005; Ellis et al. 2011).

The P024 trial was a worldwide, prospective, randomized, multicenter trial that randomized 337 postmenopausal patients with ER+ breast cancer to receive either 4 months of neoadjuvant letrozole or tamoxifen (Eiermann et al. 2001). The primary endpoint of P024 was the percentage of patients in each treatment arm with objective response as determined by clinical palpation. Secondary endpoints included ORR determined by mammogram and ultrasound and included the percentage of patients in each arm who had become eligible for BCS. The trial demonstrated a significantly higher clinical response rate for letrozole when compared with tamoxifen (55% vs. 36%; $p < 0.001$) in the intent-to-treat (ITT) population. An improved ORR for letrozole was also observed with ultrasound (35% vs. 25%; $p < 0.042$) and mammogram (34% vs. 16%; $p < 0.001$). The higher response rate assessed by clinical palpation translated into a significantly higher rate of women undergoing BCS in tumors that had initially been considered unsuitable for this procedure (45% vs. 35%; $p = 0.022$). Median time-to-response was 66 days in the letrozole group and 70 days in the tamoxifen group, and both treatments were well tolerated.

The *Immediate Preoperative Anastrozole, Tamoxifen, or Combined With Tamoxifen* (IMPACT) trial was a randomized, Phase II, double-blind, double-dummy, multicenter trial that randomly assigned 330 postmenopausal women with ER+ operable or locally advanced, potentially operable breast cancer in a 1:1:1 ratio to receive a daily dose of

anastrozole 1 mg and tamoxifen placebo, tamoxifen 20 mg and anastrozole placebo, or a combination of tamoxifen 20 mg and anastrozole 1 mg for 12 weeks before surgery. The tumor ORR was assessed by both caliper and ultrasound. No significant differences in ORR in the ITT population between patients receiving tamoxifen, anastrozole, or the combination were seen. However, in a predefined analysis, there was a nonsignificant trend towards more patients requiring mastectomy at baseline actually receiving BCS with anastrozole than with tamoxifen (44% vs. 31%, respectively; $p = 0.23$); this difference became significant for patients deemed by their surgeon to be eligible for BCS after treatment (46% vs. 22%, respectively; $p = 0.03$). All treatments were well tolerated.

The *American College of Surgeons Oncology Group (*ACOSOG*)* Z1031 trial compared three AIs in a randomized, Phase II, neoadjuvant trial designed to select agents for Phase III investigations. Three hundred seventy-seven postmenopausal women with clinical Stage II–III ER+ breast cancer were randomly assigned to receive neoadjuvant exemestane, letrozole, or anastrozole. The primary endpoint was clinical response. No formal comparison between arms was prespecified in the statistical plan. ORR was 62.9%, 74.8%, and 69.1% for the exemestane, letrozole, and anastrozole arms, respectively. On the basis of clinical response rates, letrozole and anastrozole were selected for further investigation; however, no other differences in surgical outcome, PEPI score, or Ki67 suppression were detected. The BCS rate for mastectomy-only patients at presentation was 51%.

Results from these trials suggest that neoadjuvant endocrine therapy can be beneficial in postmenopausal patients with hormone-sensitive breast cancer and that it offers an alternative to neoadjuvant chemotherapy.

### 3.3.4 Rationale for the Efficacy Outcome Measure of Response Rate Assessed by Magnetic Resonance Imaging

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, non-registrational, neoadjuvant trials in combination with endocrine therapy (Smith et al. 2005; Ellis and Ma 2007; Baselga et al. 2009).

Guidelines for RECIST v1.1 state that MRI is the preferred modality to follow breast lesions in a neoadjuvant setting, and it has advantages over computed tomography (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 (Akazawa et al. 2006; Balu-Maestro et al. 2002; Yeh et al. 2005), including the I-SPY trial (Hylton et al. 2012). For these reasons, ORR as assessed by breast MRI has been chosen as a co-primary endpoint for this trial.

#### 3.3.4.1 Rationale for Efficacy Outcome Measure of Pathologic Complete Response

pCR is a recognized efficacy endpoint of neoadjuvant trials, especially those with neoadjuvant chemotherapy, as it has been correlated with long-term outcomes, such as event-free survival (von Minckwitz and Fontanella 2013).

In trials of neoadjuvant hormonal therapy, pCR is an unlikely event. For instance, in the neoadjuvant trial comparing everolimus plus letrozole to letrozole *plus placebo*, pCR rates were 1.4% and 0.8%, respectively (Baselga et al. 2009).

In the ongoing Phase I/II trial that combines letrozole with GDC-0032, tumor shrinkage has been observed, and some patients presented sustained partial responses. As pCR is a recognized indicator of activity to a given regimen, it would be useful to assess it as a co-primary efficacy endpoint of this trial. Furthermore, for the same trial size, this would represent a minimal increase in the minimum detected difference (MDD) of the co-primary endpoint for pCR ORR (from MDD of 12% to MDD of 13%).

In September of 2013, the FDA granted accelerated approval of *pertuzumab (*Perjeta®*), an HER2 dimerization inhibitor,* as part of a complete treatment regimen for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer in the neoadjuvant setting.

#### 3.3.4.2 Rationale for Ki67 Measurements

Ki67 is a well-established proliferation biomarker with prognostic value in ER+ breast cancer (Dowsett et al. 2011). Efficacy of endocrine therapy relies on induction of cell-cycle arrest, and during neoadjuvant treatment, Ki67 levels reflect the ability of endocrine agents to suppress proliferation (Smith et al. 2005; Ellis et al. 2011). In the neoadjuvant trial of letrozole with everolimus, by using the definition that patients with natural log (Ki67) $<1$ at Day 15 have an antiproliferative response, 57% of everolimus-treated patients were responders versus 30% in the placebo arm, with a significant p value of $<0.01$ (Baselga et al. 2009). Furthermore, the mean reduction in the percentage of Ki67-positive tumor cells at Day 15 relative to baseline was greater in the everolimus-treated patients (90.7% $\pm$3.2%) than in the placebo group (74.8% $\pm$6.8%; $p=0.0002$). In the IMPACT trial, Ki67 was assessed at baseline, on Day 15, and at surgery (Smith et al. 2005). For each treatment arm, the reduction in geometric mean Ki67 levels was significantly higher for anastrozole than for tamoxifen at both timepoints ($p=0.004$, $p=0.001$, respectively), but no differences were found between tamoxifen and the combination. In the ASCOSOG Z1031 trial (Ellis et al. 2011), although no data on Ki67 at Day 15 were available, no differences were found between treatments at baseline and at surgery (after 16–18 weeks of therapy). The geometric mean percentage change in Ki67 for each treatment was similar between the arms (anastrozole 78%, exemestane 81.2%, and letrozole 87.1%).

The issue of whether Ki67 decrease at surgery or at any timepoint during treatment correlates with long-term efficacy outcomes has been addressed in the P024 trial (Eiermann et al. 2001). Treatment with letrozole led to higher, treatment-induced reduction of Ki67 levels in the tumor at surgery (87% reduction in the letrozole arm vs. 75% in the tamoxifen arm; analysis of covariance $p = 0.0009$) based on the 185 specimens with available data on Ki67 (Ellis et al. 2003). With a median follow-up of 61.2 months, low levels of Ki67 in the biopsy at the end of treatment were significantly associated with better relapse-free survival (RFS; HR 1.4 per natural log increase in the Ki67 value, 95% CI 1.2–1.6, $p < 0.001$), and breast cancer specific survival (HR 1.4, 95% CI 1.1–1.7, $p = 0.009$). Finally, in the IMPACT trial, higher Ki67 expression after 2 weeks of endocrine therapy was statistically significantly associated with lower RFS ($p = 0.004$), whereas higher Ki67 expression at baseline was not (Smith et al. 2005).

Importantly, the Ki67 suppression in these hormonal neoadjuvant trials mirrored efficacy outcomes in large adjuvant trials: adjuvant BIG1-98 trial ($n = 8,010$) showed the superior efficacy of letrozole over tamoxifen (Regan et al. 2011), similar to the neoadjuvant P024 trial ($n = 185$); the adjuvant ATAC trial ($n = 9,366$) showed that anastrozole was better than tamoxifen and the combination of anastrozole plus tamoxifen (Cuzick et al. 2010), similar to neoadjuvant IMPACT ($n = 259$); and the adjuvant MA27 trial ($n = 7,576$) showed similar efficacy of anastrozole and exemestane (Goss et al. 2013), mirroring neoadjuvant ACOSOG Z1031 ($n = 266$). These results suggest that a biological superiority hypothesis generated by a neoadjuvant study may help the design of future adjuvant hormonal therapy trials.

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

#### 3.3.4.3 Rationale for Using the Preoperative Endocrine Prognostic Index Score

In addition to Ki67, pathologic tumor size (T1 or T2 versus T3 or T4), node status (positive or negative), and the ER status (positive Allred score 3–8 versus negative Allred score 0–2) of the surgery specimen were also determined to have independent prognostic value for relapse and death after relapse in the P024 trial (Ellis et al. 2008). A PEPI score, prognostic for RFS, which weighs each of these factors according to their associated hazard ratios, was developed and subsequently validated in an independent data set from the IMPACT trial (Ellis et al. 2008). No relapses were recorded in either trial in patients with tumors classified as T1N0 and with a PEPI score of 0 (residual tumor with a Ki67 level $\leq 2.7\%$, and with maintained ER expression) or in the rare patient with a pCR.

In this trial, the PEPI score will be derived centrally.

#### 3.3.4.4 Rationale for Assessing ORR by Clinical Breast Exam (Palpation), Mammography, and Breast Ultrasound

Objective overall response rate will also be assessed by clinical breast exam, mammography, and breast ultrasound during screening and prior to surgery. These data will allow for more direct comparison of results to other neoadjuvant trials with endocrine therapy as described in Section 3.3.3. The concurrent acquisition of ORR data with these techniques, in addition to MRI-based measures, will also provide valuable comparative information on these methods, which will be important for both future neoadjuvant studies and GDC-0032 clinical development.

#### 3.3.4.5 Rationale for Assessing Enhancing Tumor Volume by Breast Magnetic Resonance Imaging

As shown in the I-SPY trial, tumor volume measurements based on the percent of tumor with enhancing signal after contrast agent administration may be a more sensitive measure of response during neoadjuvant treatment than longest dimension measures (Hylton et al. 2012). However, there are no established response criteria for volumetric data, and the extrapolation of current one- and two-dimensional criteria to volumetric data based on a spherical model may not be appropriate given the range of tumor morphologies expected in this population of patients (Loo et al. 2011). Additionally, there are only very limited data on the clinical relevance of any particular range in change in tumor volume during the course of neoadjuvant treatment. For these reasons, changes in enhancing tumor volume as measured by breast MRI will be a secondary endpoint in the trial.

### 3.3.5 Rationale for Independent Review Facility

Due to the relatively novel nature of using MRI as an imaging endpoint, a central assessment by an IRF for the co-primary endpoint of response rate via MRI will be performed to ensure consistency across all sites participating in the study.

### 3.3.6 Rationale for Interim Safety Review

The first 20 patients will be assessed for safety following surgery and 30 days beyond. This will allow the iDMC to review all safety data during the treatment period and to evaluate any surgery complications that may be attributed to GDC-0032.

### 3.3.7 Rationale for GDC-0032 Dosage

As of 5 July 2013, 34 patients have been enrolled into the dose-escalation stage of Study PMT4979g, and 56 patients have been enrolled into the single-agent expansion cohorts at 9 mg in Stage 2 (Cohorts A-D and G). All patients received GDC-0032 in capsules. Five dose-escalation cohorts (i.e., 3, 5, 8, 12, and 16 mg daily) were tested (see Section 1.7.1). The maximal administered dose was 16 mg. To obtain more safety data on long-term tolerability, the recommended single-agent dose and schedule for the single-agent GDC-0032 expansion stage *was* 9-mg *capsules* daily.

Of the 19 efficacy-evaluable patients treated with GDC-0032 in combination with letrozole, one patient at 6 mg *capsule* had a cPR. The *PIK3CA* mutation status of this patient is unknown. Since efficacy has been observed at 6 mg *capsules*, and the long-term safety suggests that 6 mg *capsule* is better tolerated, the neoadjuvant study will utilize 6-mg GDC-0032 *capsules* in combination with letrozole.

Of the 27 efficacy-evaluable patients treated with GDC-0032 in combination with fulvestrant, 2 confirmed partial responses were observed at 6 mg *capsules* and 1 confirmed partial response at 9 mg *capsules*.

Colitis has been observed with an incidence rate of 6.2% (10/160 patients). The time (from the first dose of study treatment) to onset of colitis ranged from approximately 82–248 days as either a single agent or in combination with letrozole or fulvestrant. Most of the colitis cases have been observed at the 9-mg *capsule* dose level or higher. To mitigate late-onset adverse events, such as colitis, an intermittent dosing schedule will be applied. With the 40-hour half-life, a limited impact on efficacy is anticipated. PK modeling has shown that a schedule of 5 days on/2 days off will maintain GDC-0032 drug exposure levels within an efficacious range as assessed by various breast cancer cell lines. There has also been data presented for another PI3K inhibitor, BKM120, with a similar half-life in combination with letrozole in a Phase Ib study that demonstrated improved tolerability with similar efficacy for a schedule of 5 days on/2 days off as compared with daily continuous dosing of the PI3K inhibitor (Mayer et al. 2012).

### 3.3.8 Rationale for Biomarker Assessments

Breast cancer is a heterogeneous disease, and *PIK3CA* mutations have been shown to vary among patients (CGAN 2012). Therefore, all patients may not equally likely benefit from treatment with GDC-0032. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with *PIK3CA*-driven pathogenesis who are most likely to respond to GDC-0032. Pharmacodynamic biomarkers will be evaluated to assess the biologic activity of the addition of GDC-0032 to letrozole.

It has been suggested that not all molecular alterations in the PI3K/AKT/mTOR pathway result in pathway activation. In a comprehensive analysis of tumors from 850 patients with breast cancer, protein markers of PI3K/AKT/mTOR pathway activation (pAKT, pS6, and p4EBP1) correlated strongly with *INPP4B* and PTEN loss, to a degree with *PIK3CA* amplification but were not elevated in *PIK3CA*- MT luminal A cancers (CGAN 2012). This apparent disconnect between the presence of *PIK3CA* mutations and biomarkers of pathway activation had been previously noted (Loi et al. 2010) and stress the need to find innovative and robust predictive biomarkers to PI3K/AKT/mTOR pathway inhibiting agents (Saini et al. 2013).

Next generation sequencing (NGS) techniques, like deep genome sequencing, may offer a unique opportunity to identify such biomarkers of response. For example, using whole genome sequencing, a two base-pair deletion in the *tuberous sclerosis 1 (TSC1)* gene

was found in a patient with metastatic bladder cancer with a prolonged response (>2 years) to everolimus as single agent (Iyer et al. 2012). Among 13 additional patients with bladder cancer treated with everolimus in the same trial, those with *TSC1* mutant tumors remained on therapy longer than those with WT tumors (7.7 vs. 2.0 months, p=0.004), suggesting that mTORC-1 directed therapies may be most effective in patients with cancer whose tumors harbor *TSC1* somatic mutations. *Furthermore, interesting data was recently reported from an autopsy case study from a patient with metastatic breast cancer that received an alpha-isoform PI3K blocking agent and succumbed to her disease after a lasting clinical response (Juric et al. 2015). Extensive metastatic sampling was performed post-mortem, with the main finding being the emergence of molecular aberrations leading to loss of PTEN; thus, indicating a new mechanism of secondary resistance to PI3K blockade.* Similar approaches could be of great value when analyzing responses to agents targeting the PI3K/AKT/mTOR pathway, especially in the neoadjuvant setting.

In addition to mutational activation of proteins, levels of RNA and DNA can also activate the PI3K pathway. For example, increases in DNA copy number in receptor tyrosine kinases such as FGFR1/2 and IGF-1R, which occur at some frequency in breast cancer, can activate downstream PI3K pathway. Hormone receptor positive breast cancer can be divided into luminal A and luminal B subtype, with the luminal B subtype displaying a higher proliferative index. Therefore, profiling the RNA and DNA expression of tumors will allow intrinsic subtyping of patients enrolled onto study. In addition, PI3K transcription activation signatures may identify additional patients who could respond to PI3K inhibitors outside of *PIK3CA* mutations.

The use of circulating tumor DNA (ctDNA) to monitor response to treatment is an area of great interest. It could allow for an early, non-invasive, and quantifiable method for use in the clinical setting to identify candidates for specific therapies and monitoring of disease mutation status over time (Higgins et al. 2012). The neoadjuvant setting is ideal to prospectively test these approaches.

### 3.3.9 Rationale for Day 15 Biopsy

On-study biopsies can provide valuable information regarding target engagement and downstream pathway suppression. Assessing how GDC-0032 interacts with letrozole in this previously untreated patient population provides a unique opportunity to understand the interaction between two anti-cancer molecules. When available, FFPE tumor samples will be assessed for pathway modulation using immunohistochemistry (IHC) methodologies, and fresh frozen OCT samples will be assessed using reverse phase protein array (RPPA) technologies, or equivalent. Measurement of Ki67 after 2 weeks of continuous letrozole and GDC-0032 combination treatment versus letrozole and placebo will give a good benchmark to prior neoadjuvant studies that demonstrated a larger decrease in Ki67 at this 2-week timepoint for a combination of letrozole and everolimus as compared with letrozole and placebo (Baselga et al. 2009). This Day 15 biopsy will

also be useful in identifying potential biomarkers that may help predict a tumor response for patients treated with GDC-0032.

### 3.3.10 Rationale for Collection of Blood Sample for the Detection of Plasma Protein Biomarkers

Emerging evidence indicates that increases in levels of systemic cytokines and chemokines, such as receptor tyrosine kinase growth factors, can attenuate response to drugs, particularly targeted agents such as GDC-0032 (Wilson et al. 2012). Assays to assess the expression of soluble, systemic cytokines and chemokines from the plasma of patients will be carried out using ELISA-based mass spectrometry or equivalent methodologies.

### 3.3.11 Rationale for Collection of Blood Sample for DNA Sequencing to Identify Mutations in Plasma

There is increasing evidence that circulating DNA obtained from blood specimens of patients with cancer is representative of the DNA and mutational status of tumor cells (Diehl et al. 2008; Maheswaran et al. 2008). Assays are available that can detect the major PI3K mutations (and other cancer-related genes) in plasma, and results from this analysis will be correlated with tumor specimens.

### 3.3.12 Rationale for Collection of Blood Sample for Next Generation Sequencing

Next generation sequencing (NGS) technologies generate a large quantity of sequencing data. Tumor DNA can contain both reported and unreported chromosomal alterations due to tumorigenesis process. To help control for sequencing calls in previously unreported genomic alterations, a normal blood sample will be taken during prescreening to determine whether the alteration is somatic or germline.

### 3.3.13 Rationale for Pharmacokinetic Sample Collection Schedule

PK samples will be collected from patients with early breast cancer in this study to assess the pharmacokinetics of GDC-0032 and possible DDI between letrozole and GDC-0032 in this population. Considering the lack of DDI between GDC-0032 and letrozole upon concomitant administration in the 24 patients with metastatic breast cancer in the Phase I study (preliminary data), this drug interaction in patients with early breast cancer is unlikely. Hence, extensive PK sample collection is not needed; sparse PK sampling from patients enrolled in this study is adequate. The proposed PK sample collection schedule will also enable assessment of a concentration and response relationship to better understand the following: pharmacokinetics/pharmacodynamics (efficacy), PK/safety correlation, and population pharmacokinetics. Additional PK samples may be collected for safety concerns (e.g., severe adverse event) in order to better characterize drug levels in these patients at the time of the adverse event.

### 3.3.14 Rationale for the Collection of DNA for Exploratory Pharmacogenetic Polymorphisms

One sample (approximately 3 mL of whole blood) will be collected from all patients using K3-EDTA collection tubes. Samples will be used for the evaluation of genetic polymorphisms of drug metabolic enzymes including, but not limited to, CYP2C9, CYP3A4/5, and UGT1A1, and transporters (e.g., OATP1B1) and for genetic variants, which could contribute to potentially drug-related rash and/or colitis safety assessments (including but not limited to human leukocyte antigen [HLA]). For sample handling procedures, storage conditions, and shipment instructions, see the laboratory manual. Only in circumstances where there is concern for collection of this genetic material for above evaluations, can this assessment be considered not mandatory as part of study assessments in this study. Results of any analyses from these samples will be reported outside the clinical study report.

It is established that genetic variants of drug-metabolizing enzymes and transporters can affect the pharmacokinetics of drugs, which affects their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1, which facilitates the metabolism and excretion of SN 38 (the active metabolite of irinotecan), are at higher risk for adverse effects associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006). Preliminary results from in vitro metabolism studies with GDC-0032 suggest that they are partially metabolized by multiple Phase I cytochrome P450 enzymes, including CYP3A4. Although in vitro studies can help elucidate the roles of enzymes in the metabolism of the drug, these results are not always predictive of in vivo metabolism for a number of reasons, such as differences in drug concentrations that the enzymes encounter in vitro and in vivo. For this reason, a blood sample for DNA isolation is proposed to be collected from all patients in this study for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics or response to GDC-0032. The decision to analyze the samples will be based on a review of the pharmacokinetics and response data. Most recently, the role of HLA has been demonstrated to play an important role in the development of drug-induced rash for some drugs (carbamazepine, abacavir, and allopurinol). Therefore, evaluation of genetic variants of genes that may regulate the immune response (including but not limited to HLA) may also be investigated to characterize unusual safety responses that are not predicted by GDC-0032 pharmacokinetics.

The analysis will be performed on identifiable DNA samples, because it is necessary to link a patient's PK data with genotype. This analysis would be restricted to the evaluation of genes that may be involved in the pharmacokinetics of GDC-0032, drug metabolism, disposition, or elimination and/or response of patients who develop severe adverse reactions such as colitis or rash. Samples may be stored and analyzed up to 15 years after the completion of the study, at which time all DNA samples collected for this analysis will be destroyed.

### 3.3.15 Rationale for Patient-Reported Outcome Assessments

A PRO is "any report on the status of a patient's health condition that comes directly from the patient, without any interpretation of the patient's response by a clinician or anyone else" (FDA Guidance for Industry 2007). PRO measures are able to contextualize a patient's experience on trial, elucidating symptom and treatment burden. Since early breast cancer is often asymptomatic, the PRO objective is to evaluate and compare PROs of treatment-related symptoms, patient functioning, and the health-related quality of life between treatment arms (Lemieux et al. 2011).

The EORTC QLQ-C30 and associated breast cancer module, QLQ-BR23, were selected because they were specifically developed to assess the most salient constructs and experiences with breast cancer and its treatment. The EORTC QLQ-C30 is a widely and frequently used PRO measure in oncology trials that contains a global health status scale, functional scales (physical, role, emotional, cognitive, and social), and general cancer symptom scales/items with a recall period of 'the past week.'

The second measure, the QLQ-BR23, is a breast cancer specific modular supplement to the EORTC QLQ-C30 and includes additional functioning scales and symptom scales/items relating to breast cancer.

These instruments demonstrate strong psychometric properties, of both reliability and validity, and meet the requirements for this study (EORTC QLQ-C30 Scoring Manual, 1999; see Appendix 4). Therefore, PRO data will be collected from patients using the EORTC QLQ-C30 and modified QLQ-BR23 (Quinten et al. 2009).

## 3.4 OUTCOME MEASURES

### 3.4.1 Efficacy Outcome Measures

#### 3.4.1.1 Co-Primary Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

- Tumor ORR, via centrally assessed breast MRI via modified RECIST (Appendix 3) in all enrolled patients and *PIK3CA* MT patients.
- pCR rate in breast and axilla (total pCR) as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system (Appendix 6) by local evaluation in all enrolled patients and *PIK3CA* MT patients.

#### 3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Tumor ORR, assessed by centrally assessed breast MRI via modified RECIST (Appendix 3) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR) by local evaluation in *PIK3CA* WT patients.

The following secondary outcome measures will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of ORR, as measured by modified RECIST criteria (Appendix 3) using the following methods:
    - Breast ultrasound
    - Clinical breast exam (i.e., palpation)
    - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally derived PEPI score upon treatment with letrozole plus GDC-0032 with letrozole plus placebo
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) yoT0/is, ypNX (breast pCR)

### 3.4.2 Safety Outcome Measures

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE, v4.0
- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Serious adverse events
- Protocol-defined adverse events of special interest
- Clinically significant changes in vital signs and in clinical laboratory results during the adverse event reporting period (see Section 5.3.1)

### 3.4.3 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- HRQoL, including side-effects of therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems), and patient functioning as measured using the EORTC QLQ–C30 and the modified breast cancer module QLQ–BR23

### 3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- ORR, pCR rate, and PEPI scores according to the decrease in Ki67 after 2 weeks of letrozole plus GDC-0032 and letrozole plus placebo.
- Expression of biomarkers before, during, and after therapy. These include but are not limited to the following:
    - PI3K pathway aberrations
    - Gene signatures, including intrinsic subtyping and PI3K pathway activity
    - Hormone receptor expression levels
    - Protein and phospho-protein markers and combinations
    - Mutations within cancer-associated genes
    - Copy number alterations in cancer-related genes
    - Plasma-based protein biomarkers
    - ctDNA
- Compare the rates of BCS and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo
- The relationship between GDC-0032 concentration and tumor response and/or drug safety response
- Letrozole concentrations with and without administration of GDC-0032
- The relationship between pharmacogenetic differences in drug metabolizing enzymes and transporters and other patient-specific covariates with PK of GDC-0032 or letrozole and/or drug response
- Changes from baseline to surgery in the apparent diffusion coefficient (ADC), a marker of tumor cellularity derived from diffusion-weighted MRI
- Concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response

## 4. MATERIALS AND METHODS

### 4.1 PATIENTS

Patients for this study include postmenopausal patients with ER+/HER2– untreated, Stage I–III operable breast cancer. The size of the primary tumor should be ≥2 cm by MRI.

### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF) prior to any study-specific procedure
- Female patients
- Postmenopausal status and age $\geq$ 18 years. Postmenopausal status is defined as follows:
  - Age $\geq$ 60 years or
  - Age $<$ 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment or
  - Prior bilateral oophorectomy ($\geq$ 28 days prior to Day 1 of treatment)
- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor $\geq$ 2 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 $\geq$ 2 cm and designated as the "target" lesion for all subsequent tumor evaluations.
  - Stage I to operable Stage III breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease [e.g., large tumors, clinically positive axillary lymph nodes] signs and symptoms).
- ER-positive and HER2-negative breast cancer, as per local laboratory or regional definition
- Breast cancer eligible for primary surgery
- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for *PIK3CA* mutation status by central histopathology laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Fasting glucose $\leq$ 125 mg/dL
- Adequate hematological, renal, and hepatic function, as follows:
  - Absolute neutrophil count $\geq$ 1500/$\mu$L
  - Platelets count $\geq$100,000/$\mu$L
  - Hemoglobin $\geq$ 9 g/dL
  - Serum bilirubin $\leq$ 1.5 $\times$ the upper limit of normal (ULN)
  - Patients with known Gilbert's disease who have serum bilirubin $\leq$ 3 $\times$ ULN may be enrolled
- AST, ALT, alkaline phosphatase $\leq$ 1.5 $\times$ ULN

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq 50$ mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation:

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

- International normalized ratio (INR) $< 1.5 \times$ ULN and aPTT $< 1.5 \times$ ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2 and 3 is required. If anticoagulation is required for a prosthetic heart valve, then INR should be between 2.5 and 3.5.

- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Ability and willingness to comply with study visits, treatment, testing, and to comply with the protocol, in the investigator's judgment

### 4.1.2 Exclusion Criteria

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

- Any prior treatment for primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer
- 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 sentinel lymph node biopsy prior to study treatment
- Patients for whom upfront chemotherapy is clinically judged appropriate as optimal neoadjuvant treatment
- Patients for whom immediate surgery is indicated
- Type 1 or 2 diabetes requiring antihyperglycemic medication
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteric absorption
- History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis). *Any patient with a baseline medical condition involving the gastrointestinal (GI) tract or who may have a predisposition for GI toxicity requires prior approval from the Medical Monitor.*
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF) $> 470$ msec
- $DL_{CO} < 60\%$ of the predicted values (see Appendix 7 for calculations)

- Clinically significant (i.e., active) cardiovascular disease, uncontrolled hypertension, unstable angina, history of myocardial infarction, cardiac failure class II–IV (New York Heart Association, Appendix 5), or any other that in the judgment of the investigator could jeopardize patient safety or study outcomes
- 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
- Active infection requiring intravenous (IV) antibiotics
- Patients requiring any daily supplemental oxygen
- Clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis
- Known HIV infection
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications
- Significant traumatic injury within 3 weeks prior to initiation of study treatment
- Major surgical procedure within 4 weeks prior to initiation of study treatment
- Inability to comply with study and follow-up procedures
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

### 4.2.1 Patient Randomization

After written informed consent has been obtained and eligibility has been established, the study site will obtain a patient's identification number and treatment assignment using a permuted block randomization algorithm via an interactive voice or Web-based response system (IxRS).

### 4.2.2 Stratification

Patients will be randomized into one of the two treatment arms in a 1:1 ratio based on the following stratification factors:

- Tumor size (T1–2 vs. T3)
- Nodal status (cytologically positive vs. radiologically or cytologically negative). If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then fine needle aspiration (FNA) or core biopsy is required to confirm nodal status.

### 4.2.3 Blinding

Investigators and patients will be blinded to treatment assignment of GDC-0032 or placebo.

For emergency situations, the investigator will be able to break the treatment code by contacting the IxRS. The responsibility to break the treatment code in emergency situations resides solely with the investigator. For non-emergency situations, the investigator needs to obtain approval from the Medical Monitor to break the treatment code. Unblinding during the study will result in the withdrawal of a patient from the study. For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected, suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. The PK assay group will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed and bioanalytical methodology to employ. However, the PK scientist does not have access to the PK assay results and therefore stays blinded until the PK assay results need to be interpreted and reported. Samples from patients assigned to the comparator arm will be analyzed for letrozole. However, GDC-0032 assay will be analyzed by request (i.e., to evaluate a possible error in dosing).

## 4.3 STUDY TREATMENT

### 4.3.1 Formulation, Packaging, and Handling

#### 4.3.1.1 GDC-0032 and Placebo

GDC-0032 Drug Substance and Drug Product are manufactured according to current Good Manufacturing Practice guidelines for use in the clinical studies. Each lot of GDC-0032 for clinical studies is subjected to a series of quality control tests to confirm its identity, purity, potency, and quality.

GDC-0032 is provided for use in clinical studies as a white, film-coated, immediate-release tablet formulation of 2 mg strength.

Placebo tablets will be identical in shape and color to the 2-mg tablets of GDC-0032 and will be indistinguishable from the 2-mg tablets of GDC-0032. The ingredients in the placebo tablets are identical to those in the 2-mg tablets of GDC-0032, except for the absence of GDC-0032 active.

The GDC-0032 active and placebo tablets are packaged in high-density polyethylene bottles, are labeled for clinical use, and should not be stored above 25°C.

For further details, see the GDC-0032 Investigator's Brochure.

#### 4.3.1.2 Letrozole

Letrozole will be labeled according to regulatory requirements in each country, as well as in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and will be labeled for investigational use only. The Sponsor will provide letrozole free of charge to all study sites.

Refer to the letrozole (e.g., Femara®) Package Insert or summary of product characteristics (SmPC) for details on the formulation and storage of letrozole.

### 4.3.2 Dosage, Administration, and Compliance

#### 4.3.2.1 GDC-0032 and Placebo

Patients will receive an oral, daily dose of 4 mg (two 2-mg tablets) GDC-0032 or placebo on a schedule of 5 days on/2 days off for a maximum of 16 weeks. Patients will take GDC-0032 or placebo at the same time of day ± 2 hours, unless otherwise instructed. Patients will be instructed as to the number of tablets to take. Patients will be asked to record the time and date that they take each dose in a medication diary.

If a patient misses a GDC-0032 or placebo dose or vomits up a tablet, she should be instructed to skip that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up. Patients will be instructed to bring their medication diary to each study visit for assessment of compliance. Patients will also be instructed to bring all unused tablets to each study visit for GDC-0032 or placebo accountability.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

#### 4.3.2.2 Letrozole

Patients will receive an oral, daily dose of 2.5 mg letrozole for 16 weeks (or until time of surgery at the investigator's discretion). No dose modifications of letrozole are permitted. Any overdose or incorrect administration of letrozole should be noted on the letrozole

Administration eCRF. Adverse events associated with an overdose or incorrect administration of letrozole should be recorded on the Adverse Event eCRF.

Both GDC-0032 or placebo and letrozole should be taken together (in no particular order) at the same time each day ± 2 hours, unless otherwise instructed.

### 4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (letrozole and GDC-0032) will be provided by the Sponsor where required by local health authority regulations. The investigational site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) 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 GDC-0032

The Sponsor will offer post-trial access to the study drug (GDC-0032, letrozole, or other study interventions) 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 would not 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 untreated, postmenopausal ER+/HER2−, early stage, operable breast cancer
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for untreated, postmenopausal postmenopausal ER+/HER2−, early stage, operable breast cancer
- 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
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 7 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

GDC-0032 was metabolized primarily by CYP3A4 in HLM and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low-to-moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a pharmacokinetic DDI.

Letrozole is mainly metabolized to a pharmacologically inactive carbinol metabolite by CYP2A6 and CYP3A4 in vivo. GDC-0032, which has the potential to induce CYP3A4 based on in vitro induction studies, was administered in combination with letrozole in the expansion phase of Study PMT4979g to assess their DDI potential. Preliminary data from 10 patients in this cohort indicated that steady state plasma concentrations of both letrozole and GDC-0032, following once daily administration of the combination (2.5 mg letrozole plus 6 or 9 mg GDC-0032), were similar to historical, single-agent data suggesting lack of DDI between GDC-0032 and letrozole. These preliminary results suggest that GDC-0032 and letrozole combination may be administered without the risk of a pharmacokinetic DDI.

In vitro CYP inhibition studies in HLMs and induction studies in human hepatocytes suggested a low to moderate potential of GDC-0032 to perpetrate DDIs. A clinical DDI study with rifampin (CYP3A4 inducer) and itraconazole (CYP3A4 inhibitor), to

understand the effect of CYP inhibitors or inducers on the pharmacokinetics of GDC-0032, is currently ongoing (Study GP28617).

### 4.4.2 Prohibited Therapy

Prohibited therapy is as follows:

- **Anti-cancer therapy:** No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than letrozole permitted in this protocol) will be allowed.
- **Hormone replacement therapy**, **topical estrogens (including any intra-vaginal preparations), hormonal contraception, megestrol acetate, and selective estrogen-receptor modulators used with prophylactic intent**: If a patient is receiving these at the moment of registration, treatment should be discontinued prior to randomization.
- **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.
- **Potent CYP3A4 inhibitors:** Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole and itraconazole) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If a strong CYP3A4 inhibitor is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.
- **Potent CYP3A4 inducers:** Concomitant use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, phenobarbital) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to induce CYP3A4. If a strong CYP3A4 inducer is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.

## 4.5 STUDY ASSESSMENTS

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

### 4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log

to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases that are currently active or that were active within the previous 5 years, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.

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

### 4.5.3 Physical Examination

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems as well as weight and height (height is measured at the screening visit 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), limited, symptom-directed physical examination may be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

### 4.5.4 Vital Signs

Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Oxygen saturation is obtained by pulse oximetry after the patient has been in a seated position for $\geq$5 minutes. Obtain vital signs predose.

### 4.5.5 Electrocardiograms

Triplicate electrocardiogram (ECG) recordings will be obtained at each specified timepoint (see the schedule of assessments in Appendix 1).

### 4.5.6 Distant Sites Tumor Assessment

Baseline distant sites tumor staging procedures should be performed in alignment with National Comprehensive Cancer Network (NCCN) or national guidelines, within 28 days prior to randomization.

As a reference, as per NCCN guidelines, staging procedures are based on clinical stage:

- 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.

- For Stage IIIB and Stage IIIC: bone scan and CT of chest, abdomen, and pelvis should be conducted for all patients.

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.

### 4.5.7 Tumor and Response Evaluations

All measurable disease must be documented at screening and reassessed at subsequent timepoints as outlined in Appendix 1. Responses based on clinical breast examination, breast ultrasound, and mammography will be investigator-assessed. Whenever possible, assessments should be performed by the same evaluator to ensure internal consistency across visits. Response via breast MRI will be centrally assessed, and all assessments will be based on modified RECIST criteria (see Appendix 3).

**Clinical Breast Examination:** Assessment of primary breast tumor and regional lymph nodes must be done by physical examination (palpation) during baseline evaluation, Weeks 1, 5, 9, 13 and 16 during the treatment phase and prior to surgery. Breast tumor measurement by caliper (preferred) or rule 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.

**Mammogram:** Bilateral mammograms must be obtained at baseline within 28 days prior to enrollment and again prior to surgery. Mammographic tumor measurements are to be recorded in the eCRF.

**Breast Ultrasound:** Bilateral breast ultrasounds must be obtained at baseline within 28 days prior to enrollment. Investigator decision whether to perform unilateral or bilateral ultrasounds performed at Week 9 and prior to surgery (Week 16) may be unilateral or bilateral and per investigator discretion. If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then FNA or core biopsy is required. Sonographic tumor measurements are to be recorded in the eCRF. The tumor site may be marked with a radiopaque clip or marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy.

**Breast MRI:** Contrast-enhanced breast MRI scans will be mandatory for all study patients at baseline (within 28 days prior to enrollment) and prior to surgery (Week 16). MRI is optional at Week 9 but will be mandatory if a primary breast lesion is not

evaluable by ultrasound or if there are signs of disease progression on the Week 9 ultrasound (see Figure 6).

Breast MRI scans should not be acquired within 48 hours after biopsy, and the 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 as assessed by the central reading facility, the scan may be repeated, at least 48 hours after the first scan before the start of study treatment. Other MRI acquisition sequences, such as diffusion-weighted imaging, may be acquired during this study during the MRI scan visits for each patient. Additional MRI-derived metrics such as ADC value may provide additional insight into changes in tumor cellular composition.

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

### 4.5.8 Surgical Treatment Plan

The planned and actual surgical treatment (BCS or mastectomy) performed should be documented and reported in the eCRF. Patients should be reassessed after completion of neoadjuvant therapy and prior to surgery.

### 4.5.9 Surgical Specimen–Pathology

The co-primary endpoint of the study (pCR) will be as identified by local pathology review. Guidelines regarding pathology specimen preparation, labeling, and review are outlined in the pathology manual.

### 4.5.10 Laboratory Assessments

The following assessments will be performed at the local laboratory. The frequency of assessments is provided in Appendix 1.

- Hematology (complete blood count, including red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with differential [neutrophils, eosinophils, basophils, lymphocytes, monocytes, and other cells, *if applicable*), and platelet count.
- Coagulation (INR and aPTT/PTT)
- Fasting serum chemistry (blood urea nitrogen [BUN], creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, ALT), performed following ≥ 10-hour fast
- Fasting lipid profile and amylase (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides, amylase, and lipase) performed following a ≥ 10-hour fast

- Fasting insulin and glucose
- Glycosylated hemoglobin ($HbA_{1c}$)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)

The following assessments will be performed at a central laboratory. Instruction manuals outlining sampling procedures, storage conditions, and shipment instructions and supply kits will be provided for all central laboratory assessments:

- Mandatory tumor tissue
- 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 *PIK3CA* mutation testing as well as for other protocol-mandated exploratory assessments at baseline, Day 15, and at surgery.
- Tumor tissue should be *from the primary tumor (not lymph nodes) and* of good quality based on total and viable tumor content. Evaluation of the patient's tumor sample for adequate tumor tissue content by a central laboratory must occur prior to initiation of study treatment. A minimum of ten unstained slides from a prior diagnostic FFPE core biopsy would be required for enrollment eligibility purposes.

  Two formalin-fixed, paraffin-embedded core needle biopsies and one freshly frozen OCT core needle biopsy are required at baseline and Day 15 (Week 3).

  A formalin-fixed, paraffin-embedded tumor block from surgical resection (Weeks 17–18) is required. If a tumor block cannot be obtained for various reasons (e.g., the tumor tissue is not sufficient at surgical resection), the site should discuss with the central study team. In such cases, paraffin-embedded, unstained slides (a minimum of 20 and up to 40 unstained slides) from a surgical specimen are required at surgery (Weeks 17–18). *Except in the case of pCR, every effort should be made to obtain a fresh-frozen tumor tissue sample at surgery.*

  The specimens will be used for confirmatory central laboratory assessment of *PIK3CA* mutation status, Ki67, PTEN, ER/PgR and HER2 expression. In addition, other exploratory assessments, including but not limited to, PI3K signaling pathways may be evaluated, including protein expression and molecular profiling studies such as NGS and gene-expression.
- Plasma samples for exploratory research on candidate biomarkers include but are not limited to the following: ctDNA and plasma protein biomarkers
- Blood for NGS (if approved by local regulatory authorities)
- Blood for pharmacogenomics (if approved by local regulatory authorities)
- PK assessment

  Plasma samples will be collected to measure letrozole and GDC-0032 concentrations (see 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.

### 4.5.11 Assay Methods

#### 4.5.11.1 Mutational Analysis for *PIK3CA*

The *PIK3CA* mutation assay will be performed by a central laboratory.

Somatic mutations in the *PIK3CA* gene are found in approximately 35%–40% of ER-positive breast cancers and occur most commonly in Exons 9 and 20 *(helical and kinase domain, respectively)* in the codons encoding amino acids E542, E545, and H1047 (Saal et al. 2005). Real-time polymerase chain reaction (RT-PCR) assays that amplify exons that are commonly mutated in *PIK3CA* offer a sensitive and quantitative method to detect mutations from a tumor specimen. DNA will be extracted from tumor samples and subjected to allele-specific PCR assays that detect the WT allele, as well as to assays for nucleotide substitutions that include but are not limited to the following amino acid changes: R88Q, N345K, C420R, E542K, E545K/A/G/D, E546K/E/R/L, M1043I, H1047R/L/Y, H1049R. Following histopathological review, samples with $<10\%$ tumor content may not be evaluable for the *PIK3CA* assay. Samples will be run on cobas z480 analyzer, and *PIK3CA* mutation status (mutant or WT) will be made using appropriate cutoffs and automated software.

A designation of *PIK3CA* status unknown will be assigned to a sample wherein any one of the predefined mutations was not conclusively assessed.

#### 4.5.11.2 Pharmacodynamic Biomarker Assays in Tumor Tissues

Ki67 antigen is an important cell cycle-related nuclear protein that is expressed by proliferating cells in all phases of the active cell cycle (G1, S, G2, and M phase). As such, it is a useful marker of the proliferative state of a tumor. Ki67 protein levels will be determined by IHC through the use of standard techniques.

PI3K pathway, and other pro-survival, biomarkers will be tested in the fresh tumor biopsies by IHC including but not limited to phospho-S6, phospho-AKT, phospho-4EBP1, and phospho-ERK. If tissue quantity permits, change in expression of pathway biomarkers will be measured by the RPPA using OCT fixed tissue. The basis of the technology is to immobilize small amounts of lysate from a tumor biopsy sample in serial dilution on a microarray slide. Multiple samples are thus arrayed on a slide and can be probed with antibodies that detect a particular phospho-epitope. Using this technology, we will profile approximately 80 key signaling nodes representing a number of pathways known to be dysregulated in cancer, including receptors in the HER family, multiple components of PI3K/mTor signaling, as well as key members of the RAS/MAP kinase pathway.

#### 4.5.11.3 Analysis of Phosphatase Tensin Homolog Expression

PTEN status will be examined by IHC using a protocol that has been validated for specificity using several available cell line controls at a central laboratory. Tumor specimen will be scored only if appropriate staining is observed in internal control stromal or normal (non-tumor) tissue elements.

#### 4.5.11.4 Confirmation of Estrogen Receptor, Progesterone Receptor, and HER2 Status

ER, PR, and HER2 status will be determined at a central laboratory according to the American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) guidelines.

#### 4.5.11.5 Circulating Tumor DNA Analysis

ctDNA will be extracted from plasma samples collected from patients and used for the detection of oncogenic mutations using appropriate technologies. The prevalence of the mutations measured at baseline and post-treatment may provide information on response or resistance to therapy.

#### 4.5.11.6 Messenger RNA Expression Profiling

In cases where there is sufficient archival tissue to isolate RNA, gene expression will be performed using gene expression assays conducted on the NanoString platform or equivalent. Analysis may include but is not limited to a panel of genes important for intrinsic subtyping, breast cancer biology, and PI3K signaling. The goal will be to generate a database of expression status to examine whether there are gene expression patterns that are associated with clinical response to GDC-0032.

#### 4.5.11.7 Next Generation Sequencing

In cases where there is sufficient material to isolate DNA, NGS will be performed using NGS platforms, such as Illumina or equivalent. The goal will be to determine whether the percentages of genetic mutations are associated with clinical response to GDC-0032.

#### 4.5.11.8 Copy Number Analysis

The level of copy number alterations in cancer-related genes may be determined using DNA-based technologies, either cytogenetically using chromosomal in situ hybridization (ISH), using next-generation sequencing platforms or by RT-PCR-based or equivalent technologies. For cytogenetic assays, detection may be either fluorescence-based (fluorescence in situ hybridization assay) or chromogenic-based (chromogenic in situ hybridization). Increased copy number of PI3K pathways activating genes may provide information on response or resistance to therapy.

#### 4.5.11.9 Plasma Biomarker Analyses

Assays to assess the expression of soluble, systemic cytokines, and chemokines from the plasma of patients will be carried out using appropriate methodologies, such as enzyme-linked immunosorbent assay (ELISA)-based or mass spectrometry-based or equivalent technologies.

#### 4.5.11.10 Plasma Pharmacokinetic Samples

Plasma GDC-0032 and letrozole samples will be analyzed using a validated liquid chromatography tandem mass spectrometry.

After the plasma samples are analyzed, any remaining samples may be used for exploratory metabolite profiling and identification, ex vivo protein binding, and PK, or pharmacodynamic assay development purposes.

#### 4.5.11.11 Pharmacogenetic Polymorphism Assay

If approved by the local regulatory authority, gene mutations will be assayed using multiplex PCR, allele-specific PCR, direct sequencing, or other acceptable methods. Results may be correlated to population PK parameters or other clinical measures in order to better understand the impact of genetic variants on drug metabolism, exposure, adverse events, and/or response.

A sample will also be utilized as a source of normal DNA to determine whether sequence variants in the *PIK3CA* gene and in other relevant oncogenes in the tumor DNA are somatic mutations or single nucleotide polymorphisms.

#### 4.5.11.12 Electrocardiograms

Triplicate ECG recordings will be obtained at each specified timepoint (see the schedule of assessments in Appendix 1).

#### 4.5.11.13 $DL_{CO}$ Testing

A diffusion capacity of the lung for carbon monoxide ($DL_{CO}$) test will be required at baseline and at the end of study-drug treatment (prior to surgery) for all patients. The $DL_{CO}$ test should be repeated if there is clinical suspicion of pneumonitis. Further guidance regarding $DL_{CO}$ testing is contained in Appendix 7 and in the management guidelines for pneumonitis (Section 5.1.1.2).

#### 4.5.11.14 Osteoporosis Assessment and Monitoring

Treatment with aromatase inhibitors results in bone loss due to estrogen deficiency (Gaillard and Stearns 2011). For patients who have a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis, a bone mineral density assessment will be required at baseline prior to initiating study treatment. Baseline bone mineral density will be measured via dual-energy X-ray absorptiometry (DXA). DXA measurement of both the hip and lumbar spine is suggested. When either the hip or lumbar spine is not a valid skeletal site for a bone mineral density measurement, then the 33% (one-third) radius should be measured. In some patients, measurement of the hip alone could be sufficient.

Appropriate monitoring in these patients will occur per institutional guidelines. Assessment for fractures is already included as part of the scheduled physical examinations. Determination of patients who are at increased risk for osteoporosis will be per institutional guidelines. Clinical risk factors for fracture include advancing age,

previous fracture, glucocorticoid therapy, parental history of hip fracture, low body weight, current cigarette smoking, excessive alcohol consumption, rheumatoid arthritis, and conditions predisposing to secondary osteoporosis (e.g., hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease) (Kanis et al. 2005).

### 4.5.12 Patient-Reported Outcomes

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of GDC-0032. The PRO questionnaires, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

The EORTC QLQ-C30 and the Modified Breast Cancer module QLQ-BR23 questionnaires will be used to assess HRQoL, including side-effects of systemic therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems) and patient functioning during the neoadjuvant period (refer to schedule of assessments in Appendix 1 for a detailed description of timepoints) and post-surgery follow-up.

The EORTC QLQ-C30 is a widely used HRQoL measure in oncology trials with excellent psychometric properties demonstrating both reliability and validity. The measure consists of “five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale” with a recall period of “the past week” (Aaronson et al. 1993). Scale scores can be obtained for each of the multi-item scales, global health status/QoL scale, and six single items by using a liner transformation for standardization of the calculated raw score.

The EORTC QLQ-BR23 breast cancer module was first validated for use in 1995, uses a recall period of “the past week,” and is intended for use across multiple treatment modalities (i.e., surgery, chemotherapy, radiotherapy, and hormonal treatment). As this trial will include patients in the neo-adjuvant setting, the last seven items of the original BR23 questionnaire, items numbered 47–53 that deal with symptoms and side effects not relevant to the population under study, will be removed. These seven items addressed symptoms experienced by patients with metastatic breast cancer and those undergoing radiation. Therefore, in consultation with the EORTC, these items were deleted, as the validity of the measure would not be compromised by their removal. In addition, as “oral mucositis” and “skin problems” are key symptoms of this therapy not assessed by currently available tools, validated items from the EORTC item bank were added to assess the presence and bothersomeness of oral mucositis (2 items: sore mouth/tongue, difficulty swallowing) and skin problems (2 items). Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to

assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results. Scale scores can be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score.

The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. Patients must complete these instruments in the clinic (cannot be taken home) prior to any healthcare provider interactions (i.e., prior to administration of study drug and prior to any other study assessment) to ensure that the validity of the instruments are not compromised and to ensure that data quality meet regulatory requirements.

Refer to Appendix 4 for the EORTC QLQ-C30 and the modified QLQ-BR23.

### 4.5.13 Samples for Clinical Repository

All residual samples (or leftover biologic samples after protocol-defined studies are completed) obtained during the study (FFPE, fresh-frozen, plasma, etc.) will be stored in an academic central repository. The specimens in the study repository will be made available for future biomarker research towards further understanding of treatment with GDC-0032, of breast cancer, related diseases, and adverse events, and for the development of potential, associated diagnostic assays. The implementation of study repository specimens is governed by the Study Steering Committee, with guidance from a dedicated Translational Research Committee to ensure the appropriate use of the study specimens.

All biomarker specimens will be retained for new research related to this study and/or disease in accordance with the recommendations and approval of the Study Steering Committee. Samples will be only destroyed if required by local laws relating to the collection, storage, and destruction of biological specimens.

Specimens will be stored up to 15 years or until they are exhausted. The storage period will be in accordance with the institutional review board/ethics committee (IRB/EC)-approved ICF and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

#### 4.5.13.1 Confidentiality

Patient medical information associated with biologic specimens is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from biologic specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using biologic specimens will be available in accordance with the effective Translational Reseach Committee policy on study data publication.

## 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

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.

### 4.6.2 Study Treatment Discontinuation

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

- Pregnancy
- Disease progression
- Unacceptable toxicity

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 Conditions for Terminating the Study

Both the Sponsor and the investigator reserve the right to terminate their participation in the study under the circumstances agreed upon in the site agreement. Should this be necessary, both parties will arrange the procedures on an individual basis after review and consultation. In terminating the study, the Sponsor and investigator will assure that adequate consideration is given to the protection of the patients' interest.

# 5. ASSESSMENT OF SAFETY

## 5.1 SAFETY PLAN

GDC-0032 is not approved and is currently in early clinical development. Thus, the entire safety profile is not known at this time. Human experience is currently limited. The following information is based on results from ongoing clinical studies. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events, and laboratory abnormalities (see Section 5.3.5.3), defined and graded according to NCI CTCAE, v4.0. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistry and blood counts. All serious adverse events and adverse events of special interest will be reported in an expedited fashion, via fax to Austrian Breast and Colorectal Cancer Study Group (ABCSG) safety department and also captured in the electronic data capture (EDC) system. In addition, the Sponsor and the investigators will review and evaluate observed adverse events on a regular basis.

All adverse events will be recorded during the trial and for 30 days after the last dose of study treatment or until the end of study visit, whichever occurs later. Patients who have an ongoing study treatment-related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

All adverse events should be attributed by the investigator to study drug or to another clearly identified etiology by the investigator (see Table 9).

Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections.

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

### 5.1.1 Management of Specific Adverse Events of GDC-0032

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

Due to the approximately 40-hour half-life for GDC-0032, investigators should consider holding GDC-0032 for certain Grade 2 toxicities until the adverse event resolves to Grade $\leq 1$ as discussed below (e.g., stomatitis/mucositis, colitis, rash, diarrhea, pneumonitis). Certain toxicities can occur within 1–2 weeks of holding or discontinuing

GDC-0032 drug (e.g., pneumonitis, colitis, rash). In these cases, the adverse event eventually resolves. Investigators should follow management guidelines and dose modifications for toxicities as described below, including administration of topical or systemic corticosteroids as appropriate.

**Table 1 Overall Dose Modification Guideline for GDC-0032-Related Adverse Events**

| | GDC-0032 |
|---|---|
| Starting dose | 4 mg at 5 days on/2 days off |
| First reduction | 2 mg at 5 days on/2 days off |
| Second reduction | 2 mg at 3 days on/4 days off [a] |

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

#### 5.1.1.1 Management of Hyperglycemia

Metformin is the first antihyperglycemic medication of choice because of the lower risk of hypoglycemia with this agent. Because metformin in some patients may also cause diarrhea and not be well tolerated, other antihyperglycemic medications such as sulfonylureas (e.g., glimepiride, glipizide) can be used. Extra caution should be used with other drugs such as sulfonylureas because of the increased risk for hypoglycemia with these agents. Consultation with an endocrinologist can be helpful in managing hyperglycemia.

Specific dose modification and management guidelines for hyperglycemia are provided in Table 2.

**Table 2 Dose Modification and Management Guidelines for Hyperglycemia (Based on Fasting Blood Glucose)**

| Grade | Dose Modification and Management Guidelines for Hyperglycemia (based on fasting blood glucose) |
|---|---|
| Grade 2 | Initiation of an anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring will be implemented.<br>Dosing with GDC-0032/*placebo* may either be held or continued per investigator evaluation. |
| Grade 3 (asymptomatic) | GDC-0032/*placebo* dosing will be suspended and the patient will be managed as per standard of care, including implementation of additional glucose monitoring and initiation of, or an increase in, the dose of an anti-hyperglycemic therapy (e.g., metformin).<br>If the hyperglycemic event does not improve to Grade ≤ 1 within 28 days, GDC-0032/*placebo* will be permanently discontinued.<br>If the hyperglycemic event improves to Grade ≤ 1 within 28 days, GDC-0032/*placebo* dosing may resume at one dose level lower, with approval by the Medical Monitor. |

| Grade | Dose Modification and Management Guidelines for Hyperglycemia (based on fasting blood glucose) |
|---|---|
| Grade 3 (symptomatic) [a], Grade 3 (requiring hospitalization), or Grade 4 | GDC-0032/*placebo* dosing will be suspended, and the patient will be managed as per standard of care, including implementation of additional glucose monitoring and initiation of, or an increase in, the dose of anti-hyperglycemic therapy.<br>If the hyperglycemic event does not improve to Grade ≤ 1 within 28 days, GDC-0032/*placebo* will be permanently discontinued.<br>If the hyperglycemic event improves to Grade ≤ 1 within 28 days, GDC-0032/*placebo* dosing may resume at one dose level lower, with approval by the Medical Monitor. |

[a] For example, blurred vision, frequent urination, excessive thirst.

#### 5.1.1.2 Management of Pneumonitis

Patients who require any daily supplemental oxygen are not eligible for the study. Patients who have $DL_{CO}$ values <60% will be excluded from the study. Patients will be assessed for pulmonary signs and symptoms throughout the study. The $DL_{CO}$ test should be repeated if there is clinical suspicion of pneumonitis. The $DL_{CO}$ test will also be repeated presurgery after completion of study treatment. Management guidelines for patients with possible pneumonitis are listed in Table 3.

**Table 3 Dose Modification and Management Guidelines for Pneumonitis**

| Grade | Intervention | Investigations | GDC-0032 [a] Dose Adjustment |
|---|---|---|---|
| 1 | No specific therapy required. | CT scan. Consider $DL_{CO}$. [b] Repeat CT scan every 8 weeks until return to baseline. | No change. |
| 2 | Symptomatic only. Prescribe corticosteroids if cough is troublesome. | CT scan. Repeat CT scan and $DL_{CO}$ every 4 weeks until return to baseline. Consider bronchoscopy. | Interrupt GDC-0032/*placebo* treatment until improvement to Grade ≤ 1. Interrupt treatment as long as corticosteroids are being given.<br>Restart GDC-0032/*placebo* at the same dose if clinical benefit evident. Consider restarting at reduced dose if recurrent event or per discussion with Medical Monitor.<br>Discontinue treatment if recovery to Grade ≤ 1 is not evident within 28 days. |

| Grade | Intervention | Investigations | GDC-0032 [a] Dose Adjustment |
|---|---|---|---|
| 3 | Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated. | CT scan. Repeat CT scan and $DL_{CO}$ every 4 weeks until return to baseline. [c] Bronchoscopy is recommended. | Interrupt treatment until improvement to Grade ≤ 1. Restart therapy within 28 days at a reduced dose if clinical benefit is evident. Interrupt treatment as long as corticosteroids are being given. |
| 4 | Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated. | CT scan. Repeat CT scan and $DL_{CO}$ every 4 weeks until return to baseline. Bronchoscopy is recommended. | Permanently discontinue GDC-0032/*placebo*. |

Table modified from White et al. 2010.

CT = computed tomography; $DL_{CO}$ = diffusion capacity of the lung for carbon monoxide.

[a] Dose reductions per Section 5.1.1.

[b] $DL_{CO}$ may be useful to monitor the effect of interventions such as dose reduction/discontinuation and corticosteroids, in conjunction with imaging (White et al. 2010).

[c] Follow-up imaging and investigation should be coordinated with the local pulmonologist if no baseline scans are available.

#### 5.1.1.3 Management of Rash

Rash and other dermatological events should be closely monitored, and patients with severe rash should be monitored for associated signs and symptoms such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. For severe rash, dosing of GDC-0032/*placebo* should be interrupted, and patients should be treated with supportive therapy per standard of care. Use of antihistamines, as well as topical or systemic corticosteroids, may be considered (see Table 4).

**Table 4 GDC-0032 Dose Modification and Management Guidelines for Rash**

| Grade of Rash | GDC-0032/*placebo* |
|---|---|
| Grade 1 | Continue dosing at current dose and monitor for change in severity.<br>Consider prescribing topical corticosteroids [a] |
| Grade 2 | Consider holding GDC-0032/*placebo* or reducing to the next lower dose if rash is troublesome.<br>Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]). |
| Grade 3 | Hold GDC-0032/*placebo* until Grade ≤ 1.<br>Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]).<br>Consider dermatological consultation.<br>Consider obtaining photographs of rash if permitted by local regulations.<br>After rash improves to Grade ≤ 1, restart GDC-0032/*placebo* at the next lower dose upon discussion with Medical Monitor, or permanently discontinue. |
| Grade 4 | Permanently discontinue GDC-0032/*placebo*. |

AE = adverse event.

AE grading is based on NCI CTCAE, v4.0.

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

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

#### 5.1.1.4 Management of Gastrointestinal Toxicity

##### 5.1.1.4.1 Management of Diarrhea and Colitis

Patients should be closely monitored for gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain, stomatitis, and changes in stool, including checking for blood in stool if clinically indicated). Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. *Weekly patient contact (e.g., telephone call) for all events of diarrhea Grades ≥1 is recommended to closely follow until resolution of symptoms.* Gastrointestinal symptoms should be managed per protocol guidelines and institutional standard of care. For example, prompt management of diarrhea with antidiarrheal medications should be implemented. Because of the approximately 40-hour half-life of GDC-0032, investigators should hold GDC-0032/*placebo* for Grade ≥ 2 diarrhea.

Steroid-responsive diarrhea and colitis have been difficult to distinguish in patients treated with GDC-0032. All cases of colitis have been reversible with corticosteroid treatment. Prompt initiation of corticosteroids for persistent diarrhea despite antidiarrheal treatment can decrease the severity of the diarrhea and prevent the need

for hospitalizations. Patients who develop severe steroid-responsive diarrhea usually have been on GDC-0032 treatment for at least 2 months, with an average onset between 4 and 6 months of treatment. A stool culture is helpful in identifying concurrent infections, and patients have been successfully treated with concurrent steroids and appropriate antibiotics if needed.

If a patient is being treated with corticosteroids, total parenteral nutrition is discouraged as this increases the risk for severe hyperglycemia. Discontinuation of nonsteroidal inflammatory medications or other medications that exacerbate colitis are also recommended during colitis episodes.

Perforated duodenal ulcer has been observed in 2 patients (one patient at 6 mg *capsule* in combination with letrozole; another patient at 6 mg *capsule* in combination with fulvestrant). Appropriate caution should be taken with the administration of medications such as aspirin, nonsteroidal anti-inflammatory drugs, and corticosteroids that can increase the risk of gastritis, peptic ulcers, or gastrointestinal perforation.

Specific dose modification and management guidelines for diarrhea and colitis are provided in Table 5.

**Table 5 GDC-0032 Dose Modification and Management Guidelines for Diarrhea and Colitis**

| Grade of Diarrhea | Dose Modification and Management Guidelines |
|---|---|
| Grade 1 | • Manage per institutional standard of care that includes antidiarrheals.[a]<br>• For persistent Grade 1 diarrhea occurring after Cycle 2, recommend evaluation for infectious causes via stool culture.[b] For noninfectious diarrhea, consider colonoscopy to evaluate for colitis.<br>• *For any grade of diarrhea (≥1), contact patient at least weekly to monitor until resolution of symptoms. If symptoms persist beyond 2 weeks despite antidiarrheal treatment (e.g., loperamide), escalate to Grade 2 management.* |
| Grade 2 | • Hold GDC-0032/*placebo* and initially manage with antidiarrheals.[a]<br>• Obtain stool culture for infectious workup.[b] Infections (e.g., Clostridium difficile, enteric bacteria, CMV) should be treated with the appropriate antibiotic.<br>• For persistent Grade 2 non-infectious diarrhea lasting longer than 48 hours despite treatment with antidiarrheals, treat with oral corticosteroids (20–40 mg prednisone QD starting dose with taper) or budesonide 9 mg PO QD.<br>• If Grade 2 diarrhea occurred after Cycle 2, was a recurrent episode, or improved with corticosteroid treatment, resume GDC-0032/*placebo* treatment at one dose level lower upon improvement to Grade ≤ 1 and after completion of corticosteroid treatment. |

| Grade of Diarrhea | Dose Modification and Management Guidelines |
|---|---|
| | • If Grade 2 diarrhea occurred before Cycle 2, did not require corticosteroid treatment, and was an initial episode, resume GDC-0032/*placebo* treatment at the same dose upon improvement to Grade ≤ 1.<br>• For Grade 2 colitis, resume GDC-0032/*placebo* treatment at one dose level lower upon improvement to Grade ≤ 1 and after completion of corticosteroid treatment.<br>• If Grade 2 diarrhea does not improve after 48 hours of corticosteroid treatment, a colonoscopy is recommended to evaluate for other causes of diarrhea (e.g., CMV colitis). |
| Grade 3 (first episode) | • Hold GDC-0032/*placebo* and initially *treat* with antidiarrheals. [a]<br>• Obtain stool culture for infectious workup. [b]<br>• For G3 diarrhea or colitis, treat with systemic corticosteroids (prednisone 60 – 80 mg QD equivalent or solumedrol 16–20 mg IV q8hr to start). Can increase steroid dosage if diarrhea does not improve.<br>• Concurrent infections (e.g., Clostridium difficile, enteric bacteria, CMV) should be treated with the appropriate antibiotic.<br>• For patients who do not improve upon 48 hours of corticosteroid treatment, a colonoscopy is recommended to evaluate for other causes of diarrhea (e.g., CMV colitis).<br>• If diarrhea or colitis improves to Grade ≤ 1 and upon completion of any steroid taper or antibiotic treatment, resume GDC-0032/*placebo* treatment at one dose level lower. |
| Grade 3 (recurrent) or Grade 4 | • Permanently discontinue GDC-0032/*placebo*.<br>• Workup and treatment algorithm as for Grade 3 (first episode).<br>• If patient receiving endocrine therapy, upon recovery to Grade ≤ 1, can resume endocrine therapy alone. |

CMV = cytomegalovirus; IV = intravenous; PO = oral; QD = once daily; q8hr = every 8 hours; SOC = standard of care.

[a] Suggested antidiarrheals include the following: loperamide (initial: 4 mg, followed by 2 mg after each loose stool, up to 16 mg/day); diphenoxylate and atropine (Diphenoxylate 5 mg 4 times/day until control achieved [maximum: 20 mg/day], then reduce dose as needed; some patients may be controlled on doses of 5 mg/day; tincture of opium (6 mg of undiluted opium tincture [10 mg/mL]) 4 times daily.

[b] Non-infectious diarrhea can be diagnosed by stool culture with workup for various enteric bacteria and C. difficile. Fecal calprotectin is a possible marker for bowel inflammation. Blood-based CMV PCR test can also be used to detect CMV infection.

#### 5.1.1.4.2 Management of Stomatitis and Oral Mucositis

Aggressive mouth care for oral mucositis and stomatitis with mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) may also be helpful in managing symptoms, and it is recommended that these are implemented with early signs of dry mouth, Grade 1 mucositis, or Grade 1 stomatitis (see Table 6). Avoidance of spicy foods may also be helpful.

**Table 6 GDC-0032 Dose Delay and Modification Guidelines for Stomatitis and Oral Mucositis**

| Grade of Stomatitis/Mucositis | GDC-0032/*placebo* |
|---|---|
| All grades | • Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics)<br>• Diet management (e.g., avoidance of spicy foods) |
| Grade 1 | • Monitor symptoms and initiate management (see above). Re-evaluate within 48 – 72 hours. |
| Grade 2 | • Hold GDC-0032/*placebo* and manage until Grade ≤ 1.<br>• Restart GDC-0032/*placebo* at the same dose.<br>• If Grade 2 stomatitis/oral mucositis recurs, hold GDC-0032/*placebo* until Grade ≤ 1. Restart GDC-0032/*placebo* at the next lower dose. |
| Grade 3 | • Hold GDC-0032/*placebo* and manage until Grade ≤ 1. Restart *GDC-0032/placebo* at the next lower dose.<br>For Grade 3 event that was not adequately managed upon initial presentation, consider restarting at same dose upon discussion with Medical Monitor. |
| Grade 4 | • Permanently discontinue *GDC-0032/placebo*. |

### 5.1.2 Management of Abnormal Liver Function Tests

Some patients have experienced elevations of liver function tests (e.g., AST or ALT). Patients will be monitored throughout the study treatment for changes in liver function tests. Given the potential for hepatic toxicity, all patients must have adequate liver function as manifested by measurements of serum bilirubin, hepatic transaminases, and alkaline phosphatase for initial and continued dosing. Separate criteria for eligibility, continued dosing, and DLT are given for patients with hepatic metastases and Grade 2 hepatic transaminase and/or alkaline phosphatase levels at baseline to allow safety testing to be adequately assessed in this patient group.

For new abnormal liver function tests (e.g., elevated AST or ALT), a standard clinical work-up to understand the etiology of the abnormality should take place per local guidelines. In many cases, elevated liver function tests may be a result of liver metastases, concomitant medications, or biliary obstruction. Dose modifications for elevated liver function tests are described in Table 7.

### 5.1.3 Management of Asymptomatic Lipase and/or Amylase Elevations

Some patients treated with GDC-0032 have experienced asymptomatic lipase and/or amylase elevations in blood tests without any clinical or radiographic symptoms of

pancreatitis or another clear etiology for the abnormal laboratory values. Upon discussion with the Medical Monitor and after a risk-benefit assessment, investigators can consider continuing GDC-0032 therapy in such patients at the same dose or one dose level lower. Investigators should have a low threshold for interrupting GDC-0032 for any concerning clinical gastrointestinal toxicities.

### 5.1.4 Management of Other Clinically Significant Adverse Events

See Table 7 for the dose modifications for other clinically significant adverse events.

**Table 7 GDC-0032 Dose Delay and Modification Guidelines for Other Clinically Significant Adverse Events**

| Grade | GDC-0032/*placebo* |
|---|---|
| Grade 3: first event | • Hold GDC-0032/*placebo* until Grade ≤1.<br>• Consider restarting at next lower dose. |
| Grade 3: recurrent | • Hold GDC-0032/*placebo* until Grade ≤1. |
| Grade 4: non-life-threatening | • Restart at next lower dose. |
| Grade 4: life-threatening | • Permanently discontinue GDC-0032/*placebo*. |

### 5.1.5 General Guidance for Dose Modifications and Delays for Letrozole

The letrozole dose level cannot be modified. In general, the investigator can consider continuing letrozole if it is not thought to be letrozole-related.

All dose modifications should be based on the adverse event requiring the greatest modification and should be properly documented in the source documents.

### 5.1.6 Management of Increases in QT Interval

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

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

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, as this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert electrophysiologic advice be sought to confirm any ECG changes and to ascertain the

likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

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

In rare circumstances, it may be acceptable to resume study drug, at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

### 5.1.7 Safety Monitoring for Letrozole

Letrozole is a nonsteroidal AI indicated for first line treatment of hormone receptor positive, locally advanced, or metastatic breast cancer in postmenopausal women. Letrozole is also indicated for adjuvant treatment in postmenopausal hormone-receptor positive patients and for the treatment of advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

The most frequently reported adverse events in a first line, breast cancer clinical trial with letrozole were bone pain, hot flushes, back pain, nausea, arthralgia, and dyspnea. Clinically significant adverse events also include bone effects (osteoporosis and bone fractures) and hypercholesterolemia. Discontinuations for adverse events other than progression of tumor occurred in 2% of patients on letrozole. Refer to the U.S. letrozole Package Insert or SmPC for additional information.

There are no expected significant overlapping toxicities between letrozole and GDC-0032. Routine safety monitoring and periodic laboratory tests for the letrozole and GDC-0032 combination will occur throughout the study.

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and 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 ABCSG)

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

- Fatal (i.e., the adverse event actually causes or leads to death)
- 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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 (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 ABCSG safety department immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

### 5.2.3 Adverse Events of Special Interest (Immediately Reportable to ABCSG)

Adverse events of special interest are required to be reported by the investigator to ABCSG safety department 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:

- Grade 4 hyperglycemia
- Grade ≥3 symptomatic hyperglycemia
- Grade ≥2 colitis or enterocolitis
- Grade ≥ 2 diarrhea
- *Grade ≥1 diarrhea for >2 weeks after following medical management guidelines in Section 5.1.1.4*
- Grade ≥3 rash
- Grade ≥2 pneumonitis
- 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 5.3.5.5)
- Suspected transmission of an infectious agent by the study drug

## 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 additionally reported to ABCSG safety department in case they fulfill the criteria for expedited reported in accordance with instructions provided in this section and in Section 5.4–Section 5.6.

For each adverse event recorded on the Adverse Event CRF, 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

**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 until the end of study visit, whichever occurs later. After this period, investigators should report any

deaths, serious adverse events, or other adverse events of concern deemed related to prior study drug treatment or study procedures (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 8 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 8 Adverse Event Severity Grading Scale**

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

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

Note: Based on the most recent version of NCI CTCAE (v 4.0), 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 one's self, 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 9):

- 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 (where 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 9 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 | Adverse events will be considered related, unless they fulfill the criteria as specified below.<br>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.

If known, a diagnosis 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.

#### 5.3.5.1 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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.

#### 5.3.5.2 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. The progression (increase and decrease) of an adverse event must be documented in the Adverse Event eCRF.

The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

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

### 5.3.5.3 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:

- 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
- Clinically significant in the investigator's judgment

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 the 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

### 5.3.5.4 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:

- 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
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

#### 5.3.5.5 Reporting of Abnormal Liver Function Tests as Hy's Law

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 ABCSG safety department immediately (i.e., no more than 24 hours after learning of the event), either as serious adverse event or an adverse event of special interest (see Section 5.4.2).

#### 5.3.5.6 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 ABCSG safety department (see Section 5.4.2). This includes death attributed to progression of breast cancer.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used 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 of 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.

#### 5.3.5.7 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 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”).

#### 5.3.5.8 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:

- Perform an efficacy measurement for the study
- Hospitalization for respite care
- Planned hospitalization required by the protocol for breast cancer surgery
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
    - The patient has not suffered an adverse event
- Hospitalization due solely to progression of the underlying cancer
- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care
- Hospitalization for protocol mandated biopsies

#### 5.3.5.9 Adverse Events Associated with an Overdose

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 serious criteria, the event should be reported to the ABCSG safety department immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

### 5.3.5.10 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO ABCSG

Certain events require immediate reporting to allow ABCSG safety department to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to ABCSG safety department 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 ABCSG safety department within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Adverse events of special interest *(see Section 5.2.3)*
- Pregnancies

The investigator must report new significant follow-up information for these events to ABCSG safety department 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

**U.S. Medical Monitor Contact Information**

Genentech's Medical Monitor Contact Information:

Medical Monitor: [redacted], M.D., Ph.D.

Telephone No. [redacted]

Alternate Telephone No.:

**Medical Monitor Contact Information for Sites outside the United States:**
Please refer to the country/region-specific phone numbers provided in the study binder.

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

For reports of serious adverse events and adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the paper Serious Adverse Event reporting form and transmit to ABCSG safety department via fax. In addition the serious adverse event and adverse event of special interest information will be captured in the EDC system.

| | |
|---|---|
| Worldwide Sites: | ABCSG safety department |
| Fax No.: | +43 1 409 09 90 |

Relevant follow-up information should be submitted to ABCSG safety department as soon as it becomes available and/or upon request.

## 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. *With regard to the adverse event of special interest of diarrhea, it is recommended that investigators follow every adverse event of ≥Grade 1 diarrhea with weekly patient contacts (e.g., telephone calls) and follow up until resolution. Cases that do not resolve within 1–2 weeks should be aggressively managed per protocol recommendations for gastrointestinal toxicities.*

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 (SDV). For follow-up reports of serious adverse events and adverse events of special interest, investigators should record all follow up information immediately (i.e., within 24 hours) on the paper Serious Adverse Event reporting form and transmit to ABCSG safety department via fax. In addition the serious adverse event and adverse event of special interest follow-up information will be captured in the EDC system. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF and paper Serious Adverse Event form, if applicable.

All pregnancies reported during the study should be followed until pregnancy outcome, and they should be reported according to the instructions provided in Section 5.4.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor and/or ABCSG safety department 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

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (30 days after the last dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death, other serious adverse event, or adverse event of special interest occurring after the end of the adverse event reporting period, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug or the female partner of a male patient exposed to study drug.

The investigator should report these events *directly to the Sponsor 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* (see "Protocol Administrative and Contact Information & List of Investigators").

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

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

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

- GDC-0032 Investigator's Brochure
- Local prescribing information for letrozole SmPC

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.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Primary and secondary efficacy analyses will include all patients who were included in the randomization. Final analysis will be performed after last patient, last visit (LPLV) and subsequent data cleaning, with patients allocated to the treatment arm associated by randomization.

Safety analyses will include all patients who were included in the randomization and received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

## 6.1 DETERMINATION OF SAMPLE SIZE

This study is designed for testing the effect of GDC-0032 on the two co-primary endpoints in all enrolled patients and in the *PIK3CA* MT patients and plans to enroll 330 patients in total. Assuming the *PIK3CA* mutation status will not be available (unknown) for approximately 10% of the patients and the prevalence of *PIK3CA* mutant is 40%, there will be approximately 120 patients in the *PIK3CA* MT cohort.

Given that the *PIK3CA* mutation status is not a stratification factor for randomization, there might be a possible imbalance between treatment arms within the *PIK3CA* MT cohort, which may reduce the statistical power in this cohort. To ensure the study provides sufficient statistical power even when the treatment assignment is imbalanced, the sample size was calculated based on a conservative scenario by assuming that the treatment assignment imbalance in *PIK3CA* MT is 40% versus 60%. The sample size was calculated based on a chi²-test using continuity correction (Ury and Fleiss 1980).

To control an overall, two-sided, family-wise error rate under 20% *for each analysis population*, we use a two-sided significance level of 16% and 4% for the co-primary endpoints MRI ORR, and pCR, respectively.

Assuming 10% of the patients are unevaluable for the MRI ORR, approximately 300 enrolled patients and 108 patients in the *PIK3CA* MT cohort will be evaluable for analyses. This sample size allows us to detect an absolute percentage increase of 24% in MRI ORR rate in the GDC-0032 plus letrozole arm (64%) versus the letrozole-only

arm (40%; Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at 80% power and 16% two-sided significance level. The minimal detectable difference for ORR is approximately 15%.

Assuming that all patients are evaluable for pCR (i.e., approximately 330 enrolled patients and 120 in the *PIK3CA* MT cohort), this sample size provides 80% power to detect an absolute percentage increase of 18% in pCR in the GDC-0032 plus letrozole arm (19%) versus the letrozole-only arm (1%, Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at the 4% two-sided significance level. The minimal detectable difference for pCR rate is approximately 13%.

If the prevalence of the *PIK3CA* mutation is lower than assumed, if there is more substantial treatment assignment imbalance in the *PIK3CA* MT cohort than assumed, or there is an increased number of unevaluable patients for the MRI ORR, the sample size may be increased to obtain the level of power at 80%, and the enrollment may be limited to patients with *PIK3CA* MT.

## 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 incidence of study treatment discontinuation for reasons other than disease progression will be tabulated.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables, stratification factors, and other baseline characteristics will be summarized by treatment arm.

## 6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include the ITT population; that is, all randomized patients will be included in the analyses, with patients grouped according to the treatment assigned at randomization.

### 6.4.1 Primary Efficacy Endpoint

The co-primary efficacy endpoints are (1) tumor ORR, assessed by modified RECIST criteria by breast MRI (centrally assessed) and (2) the rate of pCR in breast and axilla (total pCR) after completion of study drug.

The tumor ORR will be calculated by treatment arm in all enrolled population and in *PIK3CA* MT population. Within each population, the ORR for the two treatment arms will be compared at a two-sided alpha of 16% using a Cochran Mantel-Haenszel test, stratified by tumor size and nodal status. The pCR rate will also be calculated and compared at a two-sided alpha of 4% based on the same analytical approach as ORR. The two alpha values account for a family-wise type I error rate of 20% *for each analysis*

*population*. Patients with early study termination and hence missing efficacy outcome will be considered as non-responders.

### 6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are as follows:

- Tumor ORR after completion of study treatment, assessed by modified RECIST criteria by breast MRI (centrally assessed) in *PIK3CA* WT patients.
- Rate of pCR in breast and axilla (total pCR) after completion of study drug in *PIK3CA* WT patients.

  These endpoint measures will be summarized by treatment arm and will be analyzed analogue to the primary efficacy endpoint.

The following secondary efficacy endpoints will be performed in all enrolled patients and separated by *PIK3CA* mutation status (centrally assessed):

- ORR using modified RECIST criteria by the following methods: clinical breast examination, mammography, and breast ultrasound
- Ki67 values at baseline, Week 3, and surgery (centrally assessed)
- Change in Ki67 from baseline to Week 3; baseline to surgery, and Week 3 to surgery (centrally assessed)
- PEPI score (centrally derived)
- Change in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluation of different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR)

These endpoint measures will be summarized by treatment arm and will be compared between the two treatment arms within each population based on appropriate statistical analyses: ORR will be compared using a Cochrane Mantel-Haenszel test, stratified by tumor size and nodal status; PEPI, Ki67, and tumor volume change will be compared by regression analyses, adjusted for tumor size and nodal status. All secondary endpoints will be tested at a two-sided type I error of 5%.

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

## 6.5 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, and letrozole and GDC-0032 exposure.

Verbatim descriptions of adverse events will be mapped to thesaurus terms. Adverse event data will be listed by study site, treatment arm, patient number, and study day, severity, relationship to study drug, outcome, and action taken with the study treatments. Events occurring on or after treatment on Day 1 of Week 1 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 and vital sign (heart rate, blood pressure, and temperature) data will be displayed by time, with NCI CTCAE, v4.0 Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized in tables by NCI CTCAE, v4.0 grade.

## 6.6 PHARMACODYNAMIC ANALYSES

Ki67 biomarker analyses will include patients with at least one predose and one postdose biomarker assessment, with patients grouped according to the treatment actually received.

## 6.7 PHARMACOKINETIC ANALYSES

Individual $C_{max}$ and trough plasma concentrations ($C_{min}$) of GDC-0032 and letrozole from all patients enrolled will be reported. Mean of trough plasma concentrations of GDC-0032 and letrozole will be tabulated. The population pharmacokinetics of letrozole and GDC-0032 in this study will be compared with historical single-agent pharmacokinetics to assess the potential DDI between GDC-0032 and letrozole in this population.

Additional PK analyses on metabolites of GDC-0032, letrozole, and/or other concomitant medications may be conducted as appropriate.

## 6.8 PATIENT-REPORTED OUTCOME ANALYSES

Patient-reported outcomes of breast cancer symptoms, patient functioning, and HRQoL will be assessed by the EORTC QLQ-C30 and the modified Breast Cancer module (QLQ-BR23)

Summary statistics (mean, standard deviation, median and range) of linear transformed scores will be reported for all the items and subscales of the EORTC QLQ-C30 questionnaire, and the modified QLQ-BR23 according to the EORTC scoring manual guidelines for each assessment time point. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) of items and subscales over time will be provided for each treatment arm from the baseline assessment.

Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results.

Completion and compliance rates will be summarized at each timepoint by treatment arm with reasons for missing data. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses. The number and proportion of patients who improved, worsened, or remained stable for all of the symptom and functional domains, global QoL, and single items of the EORTC QLQ-C30 and QLQ-BR23 will be summarized.

## 6.9 EXPLORATORY ANALYSES

Additional details on analyses will be specified in the SAP.

## 6.10 INTERIM ANALYSES

The iDMC will conduct interim analyses to review the unblinded safety data after the first 20 patients have either 1) finished the 30-day follow-up visit after the surgery, or 2) been in the study for 20 weeks after the randomization date (for those who do not receive the surgery), whichever occurs first. All available information of all enrolled patients with all available assessments at the respective timepoint will be included in the interim analyses. In addition, the iDMC or the Medical Monitor may request additional ad hoc meetings of the iDMC at any time during the study to review safety data.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

ABCSG will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, ABCSG and/or all involved clinical research associates (CRAs) will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

ABCSG will produce a Data Management Plan that describes the quality checking to be performed on the data. The Sponsor will perform oversight of the data management of this study, including review of the ABCSG's data management plan and corresponding specifications. Data will be transferred electronically from ABCSG to the Sponsor at the end of the study and whenever otherwise contractually agreed, and the Sponsor's standard procedures will be used 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 at ABCSG and records retention for the study data will be consistent with the ABCSG's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff. Original PRO questionnaires will be kept in the patient's medical record as source documentation.

## 7.2 DATA(BASE) MANAGEMENT

ABCSG Clinical Data Management will check all e-forms for plausibility and consistency by automatic edit checks and manual data review according to study-specific data management plan (DMP). If necessary, web-based data queries (data clarification requests [DCRs]) will be generated and subsequently visible for the investigators, dedicated site staff, responsible CRAs, and responsible ABCSG staff. For those eCRFs which pass all verification procedures and are regarded as correct and complete, they will be frozen subsequently by ABCSG clinical data management. Consequently, no further data entries or changes on frozen eCRFs are possible. The status of frozen eCRFs is flagged by the specific icon.

Clinical Data Management ensures that the database is corrected for the following eCRF issues without immediate notification to site staff (self-evident corrections). Notification of site staff is provided via a specific report after final data cleaning procedures and before final data confirmation by the investigator or a designee:

- misspellings/typing errors that do not change the meaning of the word
- location of data recorded at an incorrect variable field or eForm (e.g., moving lab data from general comments to the appropriate lab table)
- standard time to 24-hour clock
- correction of date format, if required (dd/mm/yyyy)
- if equivalent units of terms are recorded instead of the acceptable ABCSG standard
- data changes due to plausibility checks and eCRF content (e.g., combination of several variables and/or eCRFs)

All data management workflows are described in detail in the relevant SOPs and working instructions of ABCSG.

## 7.3 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using the Clinical Data Management System "MACRO," a Web-interface DATAPORT. Sites will receive training by the responsible CRAs and have access to a manual for appropriate eCRF completion (web data entry).

All eCRFs should be completed by designated, trained site staff in a timely manner, usually within 2 weeks after the patient visit. Electronic CRFs should be reviewed and respective data confirmation eCRF should be electronically signed and dated by the investigator or a designee at the end of the study.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a storage medium (compact disc [CD], digital video disk [DVD] etc.) that must be kept with the study records. Acknowledgement of receipt of the storage medium is required.

## 7.4 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

## 7.5 USE OF COMPUTERIZED SYSTEMS

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

## 7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data (if applicable), ICFs, 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 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP 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/European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

## 8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs) 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 ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved consent forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The ICF will contain a separate section that addresses the consent for optional donation of remaining samples for the clinical repository. Samples stored in the clinical repository may be used for future exploratory research. Patients will be told that they are free to refuse to donate their remaining samples to the clinical repository. If patients choose to donate remaining samples, they may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be stored in the clinical repository.

**The ICFs must be signed and dated by the patient or the patient's legally authorized representative before participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.** The eCRF contains a section to document whether the patient has signed the ICF or not.

The ICFs 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.

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs 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 ICF 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.

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the sponsor, the affiliated

groups, or contract research organizations (CROs) according to the applicable local laws and regulations, if applicable 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 Sponsor, affiliated groups, or CROs are 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 local IRB/EC. The Sponsor, affiliated groups, or CROs 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 local health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 8.4 DATA PRIVACY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique 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 only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by local 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, provided the patient has given consent.

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. The patient will have to consent to such access by signing the informed consent form.

## 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (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, ICFs, and documentation of IRB/EC and governmental (health authorities) approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

## 9.2 ON SITE QUALITY CONTROL (MONITORING)

During the study, CRAs will visit their respective sites on a regular basis as outlined in the study specific monitoring plan (MP) and all other relevant specifications, in order to guarantee adherence to the protocol and to the principles of GCP and to check for the progress of enrolment, adequate storage conditions of IMP and adequate drug dispensing and accounting records.

CRAs will review documented data in the eCRFs for completeness and accuracy according to the study-specific MP, subsequently flag all reviewed pages with a specific mark ("SDV done") within the EDC system "MACRO," Web-interface DATAPORT, developed by [redacted] The CRAs will raise data queries ("DCRs") in cases of missing source data or incorrect data entries. Immediately after electronic issue of the queries, they become visible to the investigator, the clinical data managers, and the ABCSG clinical safety officers ("raised DCRs"). CRAs and/or clinical data managers and/or ABCSG clinical safety officers will follow up with trial site personnel until final data query resolution.

## 9.3 PROTOCOL DEVIATIONS

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

## 9.4 SITE INSPECTIONS

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

## 9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech and will be managed by Genentech in collaboration with the Breast International Group (BIG), ABCSG, and the SOLTI Breast Cancer Research Group. Genentech in collaboration with BIG, ABCSG, and SOLTI will provide clinical operations management, data management, and medical monitoring. Approximately 110 U.S. and international sites will participate to enroll approximately 330 patients.

An iDMC will be in place throughout the study and will provide oversight of safety and efficacy analyses (see Section 3.1.2).

After written informed consent has been obtained, the study site will obtain the patient's screening number from the IxRS system. Once eligibility has been established, the patient will be enrolled, and the study site will obtain the patient's identification number from the IxRS. Once results of the tissue analysis are made available, the patient will be randomized, and the site will obtain the blinded treatment assignment from the IxRS. The IxRS will manage GDC-0032/placebo drug inventory at all sites and letrozole drug inventory at all study sites outside the United States. IxRS will be required to randomize patients, to monitor enrollment and patient status, and to manage study treatment requests and shipments.

Patient data will be recorded via an electronic data capture (EDC) system from [redacted] ([redacted], United Kingdom), which will be managed by ABCSG using eCRFs (see Section 7.2).

Central laboratories, including Genentech and Genentech collaborators, will be used for *PIK3CA* mutation detection, Ki67, and PTEN status and/or will provide kits for PK, pharmacogenomic, tissue, whole blood, and plasma sample analyses to be conducted at central laboratories, Genentech, or Genentech collaborators.

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

## 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

| Study procedures | Screening | *Treatment Phase* | | | | | | | | Surgery [a,f] | Post-Surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | *W7* | W9 | *W11* | W13 | W16 (Presurgical Visit) | W17–W18 (Surgery) | 4 Weeks (±1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | *43 (±2)* | 57 (±2) | *71 (±2)* | 85 (±2) | 106–112 | 113–126 | |
| Informed consent [a] | x | | | | | | | | | | |
| Medical history and demographic data [b] | x | | | | | | | | | | |
| Physical examination [c] | x | | | x | | x | | x | x | | x |
| Clinical breast and regional lymph node examination | x | x | | x | | x | | x | x | | |
| Vital signs [d] | x | x | x | x | | x | | x | x | | x |
| ECOG Performance Status | x | x | x | x | | x | | x | x | | x |
| 12-Lead ECG [e] | x | | x | | | | | | | | |
| Mammography | x | | | | | | | | x | | |
| Breast ultrasound and axillary lymph node status [f] | x | | | | | x | | | x | | |
| Breast MRI [g] | x | | | | | | | | x | | |
| Collection of tumor samples [h] | x | | x | | | | | | | x | |
| Confirmation of receipt of adequate tissue for *PIK3CA* assessment | x | | | | | | | | | | |
| CBC with differential and platelet count [i] | x | x | | x | | x | | x | x | | x |

# Appendix 1
# Schedule of Assessments (cont.)

| Study procedures | Screening | *Treatment Phase* | | | | | | | | Surgery [a,f] | Post-Surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | *W7* | W9 | *W11* | W13 | W16 (Presurgical Visit) | W17–W18 (Surgery) | 4 Weeks (±1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | *43 (±2)* | 57 (±2) | *71 (±2)* | 85 (±2) | 106–112 | 113–126 | |
| Fasting serum chemistry [j] | x | x | | x | | x | | x | x | | x |
| Glycosylated hemoglobin ($Hb_{A1c}$) | x | | | | | | | | | | |
| Fasting insulin and glucose [k] | x | x | | x | | x | | x | x | | x |
| Fasting lipid profile and amylase [l] | x | | | x | | | | x | x | | x |
| Coagulation (INR and aPTT) | x | | | x | | x | | x | x | | x |
| Urinalysis (laboratory) [m] | x | | | x | | x | | | x | | x |
| $DL_{CO}$ [n] | x | | | | | | | | x | | |
| Bone mineral density test [o] | x | | | | | | | | | | |
| Blood sample for plasma protein biomarkers [p] | | x | | | | x | | | x | | *x* |
| Blood sample for ctDNA [q] | | x | | | | x | | | x | | *x* |
| Blood sample for NGS [r] | | x | | | | | | | | | |
| Pharmacogenomic sample [s] | | x | | | | | | | | | |
| Concomitant medication [t] | x | x | x | x | | x | | x | x | | x |
| Adverse events | x | x | x | x | *x* | x | *x* | x | x | | x |
| Inclusion/exclusion criteria [u] | x | | | | | | | | | | |
| Visit with breast surgeon (may occur from Week 13) | | | | | | | | x | | | |
| Surgery [v] | | | | | | | | | | x | |

# Appendix 1
# Schedule of Assessments (cont.)

| Study procedures | Screening | *Treatment Phase* | | | | | | | | Surgery [a,f] | Post-Surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | *W7* | W9 | *W11* | W13 | W16 (Presurgical Visit) | W17–W18 (Surgery) | 4 Weeks (±1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | *43 (±2)* | 57 (±2) | *71 (±2)* | 85 (±2) | 106–112 | 113–126 | |
| Randomization | x | | | | | | | | | | |
| Letrozole accountability/dispensation | | x | x | x | | x | | x | x | | |
| GDC-0032/placebo accountability/ dispensation | | x | x | x | | x | | x | x | | |
| Patient-reported outcomes [w] | | x | | x | | x | | x | x | | x |
| Pharmacokinetic sample (see Appendix 2 ) | | x | x | | | x | | | | | |

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; $DL_{CO}$ = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; MRI = magnetic resonance imaging; NGS = next-generation sequencing.

Note: All assessments should be performed before dosing, unless otherwise stated. Some assessments may be performed outside the window indicated to accommodate holidays, unforeseen scheduling issues, or ongoing safety issues with the trial and the patient, after approval by the Medical Monitor.

[a] Perform within 28 days prior to Day 1 of Cycle 1. Signed informed consent must be provided prior to any study-specific evaluations. Assessments performed as standard of care within the timeframe may be used.

[b] Medical history includes clinically significant diseases that are currently active or that were active within the last 5 years, surgeries, cancer history (including date of diagnosis, primary tumor histology, grade, staging, prior cancer therapies, and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse. Demographic data include age, sex, and self-reported race/ethnicity.

[c] A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems as well as weight (in kilograms) and height (in centimeters; height is measured at the screening visit only). Perform symptom-directed physical examination after baseline assessment.

[d] Vital signs include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position and temperature. Oxygen saturation is obtained by pulse oximetry after the patient has been in a seated position for ≥ 5 minutes. Obtain vital signs predose.

[e] Triplicate ECG recordings will be obtained at each specified timepoint. A window of ± 30 minutes is acceptable for all timepoints. Submit all ECGs to the diagnostic facility for central review.

# Appendix 1
# Schedule of Assessments (cont.)

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[f] Baseline evaluation of axillary lymph nodes assessed with ultrasound.

[g] MRI evaluation is optional at Week 9. MRI is mandatory at Week 9 in the event that disease progression is suspected, or if the primary lesion is not evaluable by ultrasound at baseline. Send all scans to the central reading facility for evaluation.

[h] Two formalin-fixed, paraffin-embedded core needle biopsies and one freshly frozen OCT core needle biopsy are required prior to initiation of treatment (pretreatment) and also on Day 15. A formalin-fixed, paraffin-embedded tumor block from a surgical resection is required at surgery (Weeks 17–18). *Except in the case of pCR, every effort should be made to obtain a fresh-frozen tumor tissue sample at surgery.*

[i] Complete blood count includes red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells, *if applicable*), and platelet count. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[j] Fasting (≥ 10-hour fast) serum chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[k] Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[l] Fasting lipid profile includes total cholesterol, HDL, LDL, triglycerides, amylase, and lipase. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[m] Includes specific gravity, pH, glucose, protein, ketones, and blood. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[n] $DL_{CO}$ is obtained at screening and prior to surgery. The $DL_{CO}$ test should be repeated if there is clinical suspicion of pneumonitis. $DL_{CO}$ calculations are described in Appendix 7 . The hemoglobin value used for correcting $DL_{CO}$ should represent the patient's actual hemoglobin level and should be obtained within 7 days of the $DL_{CO}$ test.

[o] Baseline bone mineral density will be measured via dual-energy X-ray absorptiometry (DXA) and will need to be obtained in women with a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis. DXA measurement of both the hip and lumbar spine is suggested. When either the hip or lumbar spine is not a valid skeletal site for BMD measurement, then the 33% (one-third) radius should be measured. In some patients, measurement of the hip alone could be sufficient.

[p] Pretreatment sample for plasma protein biomarkers should be obtained prior to dosing. *This sample will also be collected prior to dosing at Week 9, Week 16, and at the 4-week post-surgical visits.* Refer to laboratory manual for more information.

[q] Pretreatment sample for ctDNA may be obtained on Day 1 prior to dosing. This sample will also be collected prior to dosing at Week 9 and at Week 16*, and at the 4-week post-surgical visits*. Refer to laboratory manual for more information.

[r] Blood for NGS will be collected if allowed by local regulatory authorities and may be obtained prior to dosing on Week 1.

[s] Blood for pharmacogenomics will be collected if allowed by local regulatory authorities and may be obtained prior to dosing on Week 1.

[t] Record all medications used by the patient within 7 days before screening (including prescription, over-the-counter, herbal remedies, and supplements).

[u] All of the study's inclusion criteria and none of the exclusion criteria should be met prior to study entry.

[v] Surgery will take place after at least 16 weeks of combination treatment (i.e., from Week 17 to Week 18), and generally no more than 4 days after the last dose of study medication.

[w] The PRO questionnaires (EORTC QLQ-C30, modified QLQ-BR23) will be completed by the patients at the investigational site. All PRO questionnaires must be administered prior to any other study assessment(s) and prior to administration of study drug.

[x] *The assessments at Weeks 7 and 11 may be by telephone contact from the site to the patient, with interview assessment of adverse events and determination if intervention is needed.*

# Appendix 2
# Schedule of Pharmacokinetic Assessments

| Visit | Timepoint | PK Assessments |
|---|---|---|
| Day 1 | 3 hours post (±60 min) letrozole and GDC-0032/placebo administration | Letrozole PK |
| | | GDC-0032 PK |
| Day 15 (+2 days) | 0 – 4 hours prior to letrozole and GDC-0032/placebo administration | Letrozole PK |
| | | GDC-0032 PK |
| | 3 hours (±60 min) post letrozole and GDC-0032/placebo administration<br>ECG before PK | Letrozole PK |
| | | GDC-0032 PK |
| Day 57 (+/–2 days) | 3 hours post (±60 min) letrozole and GDC-0032/placebo administration | Letrozole PK<br>GDC-0032 PK |

ECG = electrocardiogram; min = minutes; PK = pharmacokinetics.

Record exact time of dose administration and sample collection.

# 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 |

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 therapy in early breast cancer. Ultrasound, mammography, and clinical exam are all

[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.

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. *Per this protocol, target lesion #1 must be ≥2 cm and, if selected, target lesion #2 must be ≥10 mm.* 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 timepoint, 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

### 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

## 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.

**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.

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

## 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
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures

## EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): _____

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

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

Please go on to the next page

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

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

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

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

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

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 31. Did you have a dry mouth? | 1 | 2 | 3 | 4 |
| 32. Did food and drink taste different than usual? | 1 | 2 | 3 | 4 |
| 33. Were your eyes painful, irritated or watery? | 1 | 2 | 3 | 4 |
| 34. Have you lost any hair? | 1 | 2 | 3 | 4 |
| 35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair? | 1 | 2 | 3 | 4 |
| 36. Did you feel ill or unwell? | 1 | 2 | 3 | 4 |
| 37. Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 38. Did you have headaches? | 1 | 2 | 3 | 4 |
| 39. Have you felt physically less attractive as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 40. Have you been feeling less feminine as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 41. Did you find it difficult to look at yourself naked? | 1 | 2 | 3 | 4 |
| 42. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 43. Were you worried about your health in the future? | 1 | 2 | 3 | 4 |
| 44. Have you had skin problems (e.g. itchy, dry)? | 1 | 2 | 3 | 4 |
| 45. Did itching of your skin bother you? | 1 | 2 | 3 | 4 |
| 46. Have you had a sore mouth or tongue? | 1 | 2 | 3 | 4 |
| 47. Have you had trouble swallowing? | 1 | 2 | 3 | 4 |

Please go on to the next page

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

| **During the past four weeks:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 48. To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 49. To what extent were you sexually active? (with or without intercourse) | 1 | 2 | 3 | 4 |
| 50. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |

# Appendix 5
# New York Heart Association Classifications

## Clinical Evaluation of Functional Capacity of Patients

| NYHA | Functional Class | Description | Objective Assessment |
|---|---|---|---|
| I | Mild | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea. | No objective evidence of cardiovascular disease. |
| II | Mild | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea | Objective evidence of minimal cardiovascular disease |
| III | Moderate | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea. | Objective evidence of moderately severe cardiovascular disease. |
| IV | Severe | Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. | Objective evidence of severe cardiovascular disease. |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors

## Tumor (T)

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ |
| Tis (DCIS) | DCIS |
| Tis (LCIS) | LCIS |
| Tis (Paget) | Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted. |
| T1 | Tumor $\leq$20 mm in greatest dimension |
| T1mi | Tumor $\leq$1 mm in greatest dimension |
| T1a | Tumor $>$1 mm but $\leq$5 mm in greatest dimension |
| T1b | Tumor $>$5 mm but $\leq$10 mm in greatest dimension |
| T1c | Tumor $>$10 mm but $\leq$20 mm in greatest dimension |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors (cont.)

## Tumor (T)

| | |
|---|---|
| T2 | Tumor > 20 mm but ≤ 50 mm in greatest dimension |
| T3 | Tumor > 50 mm in greatest dimension |
| T4 | Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)[a] |
| T4a | Extension to the chest wall, not including only pectoralis muscle adherence/invasion |
| T4b | Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma |
| T4c | Both T4a and T4b |
| T4d | Inflammatory carcinoma |

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DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

Note: The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cut-off for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cut-off. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

[a] Invasion of the dermis alone does not qualify as T4.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors (cont.)

## Regional Lymph Nodes (N)

| Clinical | |
|---|---|
| NX | Regional lymph nodes cannot be assessed (e.g., previously removed) |
| N0 | No regional lymph node metastases |
| N1 | Metastases to movable ipsilateral level I, II axillary lymph node(s) |
| N2 | Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted |
| | OR |
| | Metastases in clinically detected [a] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases |
| N2a | Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures |
| N2b | Metastases only in clinically detected [a] ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases |
| N3 | Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement |
| | OR |
| | Metastases in clinically detected [a] ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases |
| | OR |
| | Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement |
| N3a | Metastases in ipsilateral infraclavicular lymph node(s) |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Regional Lymph Nodes (N)

| | Clinical |
|---|---|
| N3b | Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s) |
| N3c | Metastases in ipsilateral supraclavicular lymph node(s) |

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[a] Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pNX | Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study) |
| pN0 | No regional lymph node metastasis identified histologically |
| Note: ITCs are defined as small clusters of cells ≤0.2 mm, or single tumor cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by IHC methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated. | |
| pN0(i–) | No regional lymph node metastases histologically, negative IHC |
| pN0(i+) | Malignant cells in regional lymph node(s) ≤0.2 mm (detected by H&E or IHC including ITC) |
| pN0(mol–) | No regional lymph node metastases histologically, negative molecular findings (RT-PCR) |
| pN0(mol+) | Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC |
| pN1 | Micrometastases |
| | OR |
| | Metastases in 1–3 axillary lymph nodes |
| | AND/OR |
| | Metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| pN1mi | Micrometastases (>0.2 mm and/or >200 cells but none >2 mm) |
| pN1a | Metastases in 1–3 axillary lymph nodes, at least one metastasis >2 mm |
| pN1b | Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pN1c | Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected |
| pN2 | Metastases in 4–9 axillary lymph nodes |
| | OR |
| | Metastases in clinically detected [a] internal mammary lymph nodes in the absence of axillary lymph node metastases |
| pN2a | Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit $>2$ mm) |
| pN2b | Metastases in clinically detected [d] internal mammary lymph nodes in the absence of axillary lymph node metastases |
| pN3 | Metastases in $\geq 10$ axillary lymph nodes |
| | OR |
| | Metastases in infraclavicular (level III axillary) lymph nodes |
| | OR |
| | Metastases in clinically detected [c] ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes |
| | OR |
| | Metastases in $>3$ axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| | OR |
| | Metastases in ipsilateral supraclavicular lymph nodes |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pN3a | Metastases in ≥ 10 axillary lymph nodes (at least 1 tumor deposit > 2 mm) |
| | OR |
| | Metastases to the infraclavicular (level III axillary lymph) nodes. |
| pN3b | Metastases in clinically detected [b] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; |
| | OR |
| | Metastases in > 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| pN3c | Metastases in ipsilateral supraclavicular lymph nodes |
| **Post-treatment ypN** | |
| Post-treatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "SN" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by AND. | |
| The X classification will be used (ypNX) if no yp post-treatment SN or AND was performed | |
| N categories are the same as those used for pN | |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

AND = axillary node dissection; H&E = hematoxylin and eosin stain; IHC = immunohistochemical; ITC = isolated tumor cells; RT-PCR = reverse transcriptase/polymerase chain reaction.

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[1] Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (SN) for "sentinel node," for example, pN0(SN).

[a] "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

[b] "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine-needle aspiration biopsy with cytologic examination.

## Distant Metastases (M)

| | |
|---|---|
| M0 | No clinical or radiographic evidence of distant metastases |
| cM0(i+) | No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other non-regional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases |
| M1 | Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm |

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**Post-treatment yp M classification.** The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pre-therapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Anatomic Stage/Prognostic Groups[a]

| Stage | T | N | M[c] |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| IA | T1[c] | N0 | M0 |
| IB | T0 | N1mi | M0 |
| | T1[c] | N1mi | M0 |
| IIA | T0 | N1[b] | M0 |
| | T1[c] | N1[b] | M0 |
| | T2 | N0 | M0 |
| IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| IIIA | T0 | N2 | M0 |
| | T1[c] | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| IIIB | T4 | N0 | M0 |
| | T4 | N1 | M0 |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

| Stage | T | N | Mc |
|---|---|---|---|
| | T4 | N2 | M0 |
| IIIC | Any T | N3 | M0 |
| IV | Any T | Any N | M1 |

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Note: Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy. Post-neoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0cM0.

[a] T1 includes T1mi.

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

[c] M0 includes M0(i+); The designation pM0 is not valid; any M0 should be clinical. If a patient presents with M1 prior to NAST, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.

# Appendix 7
# Correction of Predicted $DL_{CO}$ for Hemoglobin and Alveolar Volume

All $DL_{CO}$ measurements will be obtained as per the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines (MacIntyre et al. 2005).
The predicted $DL_{CO}$ value should be corrected for both hemoglobin ($H_b$) and alveolar volume ($v_a$).

Pulmonary function test laboratories that follow the ATS/ERS guidelines should be able to provide the value for $DL_{CO}$, corrected for $v_a$. A single breath $v_a$ may be used to obtain $DL_{CO}$, corrected for va. Use the following equation to determine the predicted $DL_{CO}$, corrected for $H_b$ and $v_a$:

> Predicted $DL_{CO}$, corrected for $H_b$ and $v_a$ = [$DL_{CO}$, corrected for $v_a$] × [1.7 × $H_b$ / (9.38 + $H_b$)]

Use the formula below to determine the percentage of predicted $DL_{CO}$ value (now corrected both for $H_b$ and $v_a$):

> **% of predicted $DL_{CO}$** (corrected for $H_b$ and $v_a$) = [actual $DL_{CO}$ / (predicted $DL_{CO}$ corrected for $H_b$ and $v_a$)] × 100

# PROTOCOL

| | |
|---|---|
| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2-NEGATIVE, EARLY STAGE BREAST CANCER** |
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38/ NCT02273973 |
| **VERSION NUMBER:** | 3 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | 110184 |
| **TEST PRODUCT:** | GDC-0032 |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.D. |
| **SPONSOR:** | Genentech, Inc. |
| **DATE FINAL:** | Version 1: 23 December 2013 |
| **DATES AMENDED:** | Version 2: 9 April 2014<br>Version 3: See electronic date stamp below. |

## PROTOCOL AMENDMENT APPROVAL

| Approver's Name | Title | Date and Time (UTC) |
|---|---|---|
| [redacted] | [redacted] | 22-May-2014 21:38:07 |

## PROTOCOL AMENDMENT, VERSION 3:
## RATIONALE

Protocol GO28888 has been amended to include the following major changes:

- GDC-0032 two-mg tablet formulation information has been added.
- Information regarding the relative bioavailability of GDC-0032 capsules and tablets has been included. In summary, the GDC-0032 tablet had a 1.5-fold higher drug exposure (area under the curve; AUC) in healthy volunteers as compared to the GDC-0032 capsule. In this trial, 2-mg tablets instead of the 3-mg tablets originally proposed, will be provided and are expected to have very similar drug exposure as the 3-mg capsules used in previous clinical trials with GDC-0032.
- The requirement for taking GDC-0032 on an empty stomach has been removed. The drug exposure (AUC) for GDC-0032 in a healthy volunteer study was not affected by the consumption of a high-fat meal.
- Management guidelines for adverse events of special interest have been updated. More detailed information on the dosage of recommended corticosteroids for diarrhea and colitis has been included. In addition, extra language regarding caution with using steroids has been added.

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

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The list of abbreviations has been updated to reflect changes to the protocol.

## PROTOCOL SYNOPSIS

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

## SECTION 1.1: BACKGROUND ON THE PHOSPHATIDYLINOSITOL-3-KINASE PATHWAY

In addition, the PI3K-AKT pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling…*and Inositol Polyphosphate 4-phosphatase type II (INPP4B)*, or RAS mutations….

## SECTION 1.4: BACKGROUND ON REVERSING HORMONAL RESISTANCE BY INHIBITING THE PI3K/MTOR/AKT PATHWAY

In the setting of ER+ breast cancer, PI3K seems to play an important role in mediating hormonal resistance and ~~may be~~ *is* a viable therapeutic target.

## SECTION 1.5: BACKGROUND ON NEOADJUVANT THERAPY IN BREAST CANCER

A meta-analysis of nine randomized studies… showed no difference in … *distant* disease recurrence based upon the timing of the systemic therapy (Mauri et al. 2005).

…meta-analysis was recently conducted evaluating over 12,000 patients treated with neoadjuvant chemotherapy as part of clinical trials (Cortazar et al. 201*4*~~2~~).

## SECTION 1.6: BACKGROUND ON GDC-0032

Enhanced efficacy was demonstrated in combination with tamoxifen, another endocrine therapy used in the treatment of hormone receptor-positive ~~advanced~~ breast cancer.

## SECTION 1.7.1: Clinical Safety Data with GDC-0032

As of 5 July 2013, a total of 144 patients have been treated with GDC-0032 *capsules, in the Phase I/II PMT4979g study,* either as single agent (*n* =90, 63%) or in combination with endocrine therapy (*n* =54, 37%).

~~GDC-0032 is currently in Phase I (Study PMT4979g). Study PMT4979g is an open label, dose-escalation trial using a 3 + 3 design to assess the safety, tolerability, and pharmacokinetics of GDC-0032 administered orally daily for 28 days to patients with locally advanced or metastatic solid tumors and in combination with endocrine therapy in ER+ breast cancers.~~ As of 5 July 2013, enrollment into the dose-escalation stage of Study PMT4979g had been completed with 34 patients enrolled at *GDC-0032* doses ~~with a range of~~ *ranging from* 3 to 16 mg daily…. As of the cutoff date, a total of 53 patients ~~have~~ *had* been enrolled in the 9-mg daily dosing expansion cohorts.

As of 5 July 2013, adverse events *of any grade* that occurred in ≥10% of the 87 patients treated with daily single-agent GDC-0032 *capsules* and were *investigator*-assessed as related to GDC-0032 were as follows: …fatigue (~~34.5~~ *35*%), decreased appetite (31%), rash (25%), stomatitis (13%), vomiting (13%), and mucosal inflammation (~~11.5~~ *12*%). ~~Study- drug related~~ Grade 3 and 4 adverse events *assessed by the investigator as GDC-0032 related* included hyperglycemia (~~9.4~~ *12*%), colitis (~~7.~~ *6%), rash (*5%), *diarrhea (3%), fatigue (3%),* pneumonitis (3~~.8~~%)~~, rash (including maculopapular rash with or without itching, redness, and peeling) 5.7%, asymptomatic~~*, pruritus (2%), stomatitis (2%),* increased *alanine* aminotransferase levels ~~in the blood~~ (1~~.9~~%), anemia (1~~.9~~%), increase in blood creatinine (1~~.9%), diarrhea~~*%), exfoliative rash* (1~~.9%), fatigue (1.9~~%), hypokalemia (1~~.9~~%), hypophosphatemia (1~~.9~~*%), lung infection (1*%), pneumonia (1~~.9~~*%), erythematous rash (1%), generalized rash (1%), maculopapular rash (1%) and skin exfoliation (1*%) and ~~stomatitis~~ *acute renal failure* (1~~.9~~%).

… Adverse events *of any grade and assessed by the investigator as drug related* that occurred in ≥ 10% of the 27 safety-evaluable patients assessed as related to GDC-0032 were *…rash (30%),…* mucosal inflammation (~~18.5%), rash (18.5~~ *19*%)*… and* dry mouth (11%)~~. dry skin (11%) and muscle spasms (11%). Study - drug related.~~ Grade 3 and 4 adverse events ~~included~~ *assessed by the investigator as GDC-0032 related include* diarrhea (11%), mucosal inflammation (7~~.4~~%), increased amylase ~~in the blood~~ (~~3.7~~ *4%), hyperglycemia (4*%), increased aspartate aminotransferase (AST) ~~in the blood~~ *(4%), stomatitis* (3.7%), increased *blood* alkaline phosphate ~~in the blood~~ (~~3.7~~ *4*%), fatigue (~~3.7~~ *4*%), increased gamma-glutamyltransferase in the blood (~~3.7%), hyperglycemia (3.7~~ *4*%), hypokalemia (~~3.7~~ *4*%), increased lipase in the blood (~~3.7~~ *4*%), *and* papilloedema (~~3.7%) and stomatitis (3.7~~ *4*%).

…Adverse events *assessed by the investigator as GDC-0032 related and of any grade* that occurred in ≥ 10% of the 27 patients and were assessed as related to GDC-0032 were diarrhea (~~46~~ *48*%), hyperglycemia (~~32~~ *33*%), nausea (~~32~~ *33*%), decreased appetite (~~25~~ *26*%), fatigue (~~25~~ *26*%), rash (~~21~~ *26*%), stomatitis (~~21~~ *22*%), asthenia (~~18~~ *19*%), muscle spasms (~~14~~ *15*%), vomiting (~~14~~ *15*%), dysgeusia (11%), gastroesophageal reflux disease (11%) and mucosal inflammation (11%). ~~Study - drug related~~ Grade 3 and 4 adverse events *assessed by the investigator as related to GDC-0032* included hyperglycemia (~~14~~ *15*%)...

## SECTION 1.7.1.1: Preliminary Pharmacokinetics

*Preliminary data from a healthy volunteer study showed that the 3-mg GDC-0032 tablet produces an estimated geometric mean ratio (90% CI) of 196% (177.1 –217.0) for $C_{max}$ and 152.2% (141.9 –163.2) for AUC time 0 to infinity ($AUC_{0\text{-}inf}$) when compared with the 3-mg Phase I capsule. For this reason, a new 2-mg tablet has been formulated to deliver GDC-0032 exposure similar to the 3-mg capsule formulation.*

*The drug exposure (AUC) for GDC-0032 in a healthy volunteer study was minimally affected by the consumption of a high-fat meal. Therefore, GDC-0032 may be taken without regard to the timing of the administration of food.*

## SECTION 1.8: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Nonclinical data support… endocrine therapy in patients with hormone receptor-positive~~,~~ ~~advanced~~ breast cancer.

As of 5 July 2013, efficacy data are available for 24 patients treated with GDC-0032 *capsules* in combination with letrozole…

## SECTION 2.1: EFFICACY OBJECTIVES

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of locally assessed ORR *as measured by modified RECIST criteria (Appendix 3*) using the following methods…
- Compare the centrally ~~assessed~~ *derived*, preoperative endocrine prognostic index (PEPI) score upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo.

## SECTION 3.1: DESCRIPTION OF STUDY

Letrozole at 2.5 mg will be dosed once daily plus either GDC-0032 at ~~6~~ *4* mg *(two 2-mg tablets)* or placebo on a 5 – days-on/ 2 – days-off schedule for a total of 16 weeks (see Figure 5).

Blood sample for exploratory endpoint analysis will be collected *on Day 1 prior to dosing,* ~~at screening,~~ at Week ~~3~~ *9*, and prior to surgery.

## FIGURE 5: Study Schema

Figure 5 has been revised to reflect changes to the protocol.

## SECTION 3.1.1: Surgery

The patient should be evaluated at baseline and after Week 13 of treatment for planning the surgical procedure (BCS or mastectomy), and both ~~physician recommendation and final patient decision~~ *the planned and actual surgical treatment* ~~and final patient decision~~ should be documented in the electronic Case Report Form (eCRF).

## SECTION 3.1.2: Independent Data Monitoring Committee

The IDMC will ~~convene for an interim~~ *review the unblinded* safety ~~analysis to evaluate safety and pharmacokinetics~~ *data* after the first 20 patients have ~~completed surgery and have had~~ *either 1) finished the* 30-day~~s~~ ~~of~~ follow-up *visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery), whichever occurs first.* ~~The IDMC will create and review unblinded, pooled summaries of the safety and available PK summaries (all interim analyses)~~….

~~The IDMC will share results from interim safety analyses with the study team. The study team will share interim safety results with study investigators as needed for the conduct of the study and the safety of the patients. Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections.~~

### SECTION 3.3.1: Rationale for Conducting the Study in the Neoadjuvant Setting

Over the past 10 years, four major classes of breast cancer (Luminal A, Luminal B, HER2-enriched, and basal-like) ~~and a Normal Breast like group~~ have been identified and intensively studied…

### SECTION 3.3.2: Rationale for Patient Population

Important findings in trials with drugs targeting mTOR, like everolimus, ~~produce~~ *confirm* a *previously identified* pharmacodynamic paradox: while inhibiting mTOR, they lead to an upregulation of the pAKT, resulting in feedback PI3K/AKT/mTOR pathway activation *through an insulin-like growth factor-1 receptor (IGF-1R) mediated feedback loop* (Tabernero et al. 2009).

### SECTION 3.3.4.3: Rationale for Using the Preoperative Endocrine Prognostic Index Score

In this trial, the PEPI score will be ~~assessed~~ *derived* centrally.

### SECTION 3.3.7: Rationale for GDC-0032 Dosage

*All patients received GDC-0032 in capsules.* Five dose-escalation cohorts (i.e., 3, 5, 8, 12, and 16 mg daily) were tested *(see Section 1.7.1).*

~~In Study PMT4979g, as of the 5 July 2013 data cutoff date, there were 87 safety evaluable patients treated with single agent GDC 0032 *capsules* (3 – 16 mg daily). A total of 97% of patients experienced at least one adverse event per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 (NCI CTCAE v4.0). The most frequently reported adverse events *of any grade*, occurring in ≥10% safety evaluable patients regardless of causality, were diarrhea (55%), fatigue (49%), nausea (47%), decreased appetite (39%), hyperglycemia (38%), vomiting (28%), dizziness (22%), rash (22%), dyspnea (18%), hypokalemia (18%), pyrexia (17%), cough (16%), anemia (13%), dehydration (13%), headache (13%), stomatitis (13%), AST increased (12%), mucosal inflammation (12%) and pruritis (10%).~~

~~As of 5 July 2013, 54 patients have been treated with GDC 0032 *capsules* in combination with endocrine therapy with either letrozole (Cohort E) or fulvestrant (Cohort F) at either 6 mg or 9 mg dose levels. No DLTs were observed during dose escalation in either Cohorts E or F. Expansion cohorts at the 6 mg dose level were enrolled to obtain more safety data on long term tolerability. Fifty (93%) of the 54 safety evaluable patients experienced at least one adverse event that was assessed as related to GDC 0032.~~

~~Of the 54 patients, 17 patients were treated with GDC-0032 *capsules* plus letrozole. Adverse events *of any grade* that occurred in ≥10% of patients that were assessed as related to GDC-0032 (6mg and 9mg) were diarrhea (67%), nausea (33%), fatigue (30%), rash (30%), hyperglycemia (26%), decreased appetite (26%), stomatitis (26%), dysgeusia (22%), mucosal inflammation (19%), asthenia (15%), vomiting (15%), pruritis (15%), muscle spasms (11%), dry skin (11%), and dry mouth (11%).~~

## SECTION 3.3.8: Rationale for Biomarker Assessments

Pharmacodynamic biomarkers will be ~~assessed~~ *evaluated* to assess the biologic activity of the addition of GDC-0032 to letrozole.

## SECTION 3.4.1.2: Secondary Efficacy Outcome Measures

- Compare the centrally ~~assessed~~ *derived* PEPI score upon treatment with letrozole plus GDC-0032 with letrozole plus placebo

## SECTION 4.1.2: Exclusion Criteria

- Clinically significant (i.e., active) cardiovascular disease, ~~like~~ uncontrolled hypertension…

## SECTION 4.3.1.1: GDC-0032 and Placebo

GDC-0032 is provided for use in clinical studies as a white, film-coated, immediate-release tablet formulation of ~~3~~ *2* mg strength. ~~The tablet formulation consists of GDC-0032 active, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and Opadry 2 white film coating. All excipients used in the formulation are compendial (USP/NF/Ph. Eur/JP) grade with the exception of the film coating. The film coating consists of polyvinyl alcohol part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc, and these ingredients are compendial.~~

Placebo tablets will be identical in shape and color to the ~~3~~ *2*-mg tablets of GDC-0032 and will be indistinguishable from the ~~3~~ *2*-mg tablets of GDC-0032. The ingredients in the placebo tablets are identical to those in the ~~3~~ *2*-mg tablets of GDC-0032, except for the absence of GDC-0032 active.

## SECTION 4.3.2.1: GDC-0032 and Placebo

Patients will receive an oral, daily dose of *4*~~6~~ mg *(two 2-mg tablets)* GDC-0032 or placebo on a schedule of 5 days on/2 days off for a maximum of 16 weeks. Patients will take GDC-0032 *or placebo* at the same time of day ± 2 hours…

~~Unless otherwise instructed, GDC-0032 or placebo should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal).~~

## SECTION 4.3.2.2: Letrozole

*Both GDC-0032 or placebo and letrozole should be taken together (in no particular order) at the same time each day ± 2 hours, unless otherwise instructed.*

### SECTION 4.5.2: Medical History and Demographic Data

Medical history includes clinically significant diseases…and all medications… used by the patient within ~~15~~ *7* days prior to the screening visit.

### SECTION 4.5.3: Physical Examination

Any abnormality identified at baseline should be recorded on the General Medical History and ~~Baseline Conditions~~ *Vital Signs* eCRF.

### SECTION 4.5.4: Vital Signs

*Oxygen saturation is obtained by pulse oximetry after the patient has been in a seated position for ≥5 minutes. Obtain vital signs predose.*

### SECTION 4.5.11.14: Osteoporosis Assessment and Monitoring

Treatment with aromatase inhibitors results in bone loss due to estrogen deficiency *(Gaillard and Stearns 2011).*

Clinical risk factors for fracture include… and *conditions predisposing to* secondary osteoporosis….

### SECTION 5.1.1: Management of Specific Adverse Events of GDC-0032
### TABLE 1: Overall Dose Modification Guideline for GDC–0032-Related Adverse Events

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

### SECTION 5.1.1.1: Management of Hyperglycemia

~~Hyperglycemia has been observed in patients who received GDC-0032 in the single-agent Phase I study.~~

~~Patients with diabetes requiring daily anti-hyperglycemic medication or who have a fasting blood glucose level >125 mg/dL will be excluded from the study. $HbA_{1c}$ and fasting glucose levels will be monitored at baseline, and additional monitoring of fasting glucose levels during the study will be implemented, as outlined in the schedule of assessments. Patients should be instructed to report symptoms associated with hyperglycemia such as thirst, frequent urination, and blurred vision.~~

### TABLE 3: Dose Modification and Management Guidelines for Pneumonitis

Table 3 has been revised to reflect changes to the protocol.

### SECTION 5.1.1.2: Management of Pneumonitis
### TABLE 4: Dose Modification and Management Guidelines for Pneumonitis

Table 4 has been revised to reflect changes to the protocol.

### SECTION 5.1.1.3: Management of Rash
### TABLE 5: GDC-0032 Dose Modification and Management Guidelines for Rash

Table 5 has been revised to reflect changes to the protocol.

### SECTION 5.1.1.4.1 Management of Diarrhea *and Colitis*

Because of the approximately 40-hour half-life of GDC-0032, investigators should hold GDC-0032 for Grade ≥ 2 diarrhea ~~until it improves to Grade ≤ 1.~~

*Steroid-responsive diarrhea and colitis have been difficult to distinguish in patients treated with GDC-0032. All cases of colitis have been reversible with corticosteroid treatment. Prompt initiation of corticosteroids for persistent diarrhea despite antidiarrheal treatment can decrease the severity of the diarrhea and prevent the need for hospitalizations. Patients who develop severe steroid-responsive diarrhea usually have been on GDC-0032 treatment for at least 2 months, with an average onset between 4 –6 months of treatment. A stool culture is helpful in identifying concurrent infections, and patients have been successfully treated with concurrent steroids and appropriate antibiotics if needed.*

*If a patient is being treated with corticosteroids, total parenteral nutrition is discouraged as this increases the risk for severe hyperglycemia. Discontinuation of nonsteroidal inflammatory medications or other medications that exacerbate colitis are also recommended during colitis episodes.*

*Perforated duodenal ulcer has been observed in 2 patients (one patient at 6 mg in combination with letrozole; another patient at 6mg in combination with fulvestrant). Appropriate caution should be taken with the administration of medications such as aspirin, nonsteroidal anti-inflammatory drugs, and corticosteroids, which can increase the risk of gastritis, peptic ulcers, or gastrointestinal perforation.*

Specific dose modification and management guidelines for diarrhea *and colitis* are provided in Table 5.

### TABLE 6: GDC-0032 Dose Modification and Management Guidelines for Diarrhea *and Colitis*

Table 6 has been revised to reflect changes to the protocol.

### ~~SECTION 5.1.1.4.2: Management of Colitis~~

~~Data as of October 2013 show an incidence rate for colitis of 6.2% (10/160) (1 at 16 mg; 8 at 9 mg; 1 at 6 mg + fulvestrant) with onset at approximately 100 days or longer after initiation of treatment with daily GDC-0032 dosing. Some patients have developed Grade 2 or Grade 3 diarrhea, which is non responsive to anti-diarrheal medication. In some of these patients, a CT scan or colonoscopy has revealed colitis, which has resolved upon treatment with systemic corticosteroids.~~

~~For persistent Grade 2 diarrhea that does not resolve or for Grade ≥ 3 diarrhea, further evaluation should include colitis in the differential diagnosis with the appropriate work-up (e.g., abdominal/ pelvis CT scan, endoscopy with biopsy, stool cultures for cytomegalovirus, Clostridium difficile, and parasites). Grade ≥ 2 colitis should be managed by interruption of study treatment. In addition, discontinuation of nonsteroidal~~

~~anti-inflammatory medications or any other medications known to exacerbate colitis symptoms should be considered. If noninfectious colitis is suspected, treatment with corticosteroids per institutional standard of care should be considered. It is suggested that prednisone (for oral administration) or solumedrol (for IV administration) are the corticosteroids of choice in the treatment of colitis. For severe symptoms, prednisone 60 mg or equivalent may be required to control initial symptoms, and the dose should be gradually tapered. Lower doses of prednisone, oral budesonide, or mesalamine (or other 5-aminosalicyclic acid derivatives) may be considered for less severe cases of colitis.~~

~~Specific dose modification and management guidelines for colitis are provided in Table 7.~~

**~~Table 7: GDC-0032 Dose Modification and Management Guidelines for Colitis~~**

Table 7 has been deleted. Subsequent tables have been renumbered accordingly.

### SECTION 5.1.1.4.3: Management of Stomatitis and Oral Mucositis

### TABLE 8: GDC-0032 Dose Delay and Modification Guidelines for Stomatitis and Oral Mucositis

Table 8 has been revised to reflect changes to the protocol.

### SECTION 5.1.2: *Management of Abnormal Liver Function Tests*

*Some patients have experienced elevations of liver function tests (e.g., AST or ALT). Patients will be monitored throughout the study treatment for changes in liver function tests. Given the potential for hepatic toxicity, all patients must have adequate liver function as manifested by measurements of serum bilirubin, hepatic transaminases, and alkaline phosphatase for initial and continued dosing. Separate criteria for eligibility, continued dosing, and DLT are given for patients with hepatic metastases and Grade 2 hepatic transaminase and/or alkaline phosphatase levels at baseline to allow safety testing to be adequately assessed in this patient group.*

*For new abnormal liver function tests (e.g., elevated AST or ALT), a standard clinical work-up to understand the etiology of the abnormality should take place per local guidelines. In many cases, elevated liver function tests may be a result of liver metastases, concomitant medications, or biliary obstruction. Dose modifications for elevated liver function tests are described in Table 7.*

### SECTION 5.1.3: *Management of Asymptomatic Lipase and/or Amylase Elevations*

*Some patients treated with GDC-0032 have experienced asymptomatic lipase and/or amylase elevations in blood tests without any clinical or radiographic symptoms of pancreatitis or another clear etiology for the abnormal laboratory values. Upon discussion with the Medical Monitor and after a risk-benefit assessment, investigators can consider continuing GDC-0032 therapy in such patients at the same dose or one*

*dose level lower. Investigators should have a low threshold for interrupting GDC-0032 for any concerning clinical gastrointestinal toxicities.*

### SECTION 5.3.5.5: *Reporting of* Abnormal Liver Function Tests *as Hy's Law*

### SECTION 5.3.5.7: Preexisting Medical Conditions

Such conditions should be recorded on the General Medical History ~~and Baseline Conditions~~ *e*CRF.

## SECTION 5.6: POST-STUDY ADVERSE EVENTS

*The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (30 days after the last dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death, other serious adverse event, or non-serious adverse event of special interest occurring after the end of the adverse event reporting period, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug or the female partner of a male patient exposed to study drug.*

*The investigator should report these events by completing and faxing a paper Serious Adverse Event Reporting Form and fax cover sheet to Safety Risk Management using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").*

~~The investigator should report these events directly to Genentech Safety Risk Management via telephone at 1-888-835-2555.~~

## SECTION 6.4.1: Primary Efficacy Endpoint

The co-primary efficacy endpoints are (1) tumor ORR, assessed by modified RECIST criteria by breast MRI *(centrally assessed)…*

## SECTION 6.4.2: Secondary Efficacy Endpoints

- Tumor ORR after completion of study treatment, assessed by modified RECIST criteria by breast MRI *(centrally assessed)* in *PIK3CA* WT patients.

The following secondary efficacy endpoints will be performed in all enrolled patients and separated by *PIK3CA* mutation status *(centrally assessed)*:

- ORR *using modified RECIST criteria by the following methods:* clinical breast examination, mammography, and breast ultrasound…
- PEPI score (centrally ~~assessed~~ *derived*)...

## SECTION 6.10: INTERIM ANALYSES

The IDMC will conduct interim analyses to review the unblinded safety data after the first 20 patients have either 1) finished the 30-day, follow-up visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery)*, whichever occurs first*.

## SECTION 8.2: INFORMED CONSENT

The ICF will contain a separate section that addresses the *consent for optional donation of remaining samples for the clinical repository.* ~~use of remaining mandatory samples for optional exploratory research.~~ *Samples stored in the clinical repository may be used for future exploratory research.* ~~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 *donate their remaining samples to the clinical repository. If patients choose to donate remaining samples, they* ~~participate and~~ may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be *stored in the clinical repository.* ~~used for exploratory research. Patients who decline to participate will not provide a separate signature.~~

## SECTION 9.5: ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech and will be managed by Genentech in collaboration with the Breast International Group (BIG), ABCSG, and the *SOLTI* ~~Spanish~~ Breast Cancer Research Group ~~(SOLTI)~~.

## SECTION 10: <u>REFERENCES</u>

The following references have been added:

Cortazar P, Zhang L, Untch M et al. *Pathologic complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;13: 62422–8.*

*Gaillard S and Stearns V. Aromatase inhibitor-associated bone and musculoskeletal effects: new evidence defining etiology and strategies for management. Breast Cancer Res 2011;13:205.*

## APPENDIX 1: Schedule of Assessments

The Schedule of Assessments has been revised to reflect the changes to the protocol.

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

Appendix 3 has been revised to reflect changes to the protocol.

## SAMPLE INFORMED CONSENT FORMS

The sample Informed Consent Forms have been revised to reflect the changes to the protocol.

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## PROTOCOL AMENDMENT ACCEPTANCE FORM

| | |
|---|---|
| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2-NEGATIVE, EARLY STAGE BREAST CANCER** |
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38 |
| **VERSION NUMBER:** | 3 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | 110184 |
| **TEST PRODUCT:** | GDC-0032 |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.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 return the signed original of this form as instructed by your local study monitor. Please retain a copy for your study files.

**Principal Investigators:**

[redacted]

| Author(s): | Affiliation |
|---|---|
| [redacted] | [redacted], USA<br>[redacted], Belgium<br>[redacted], SOLTI Breast Cancer Research Group, Diputació 256 4º1ª 08007 Barcelona, Spain<br>[redacted], Genentech, South San Francisco, CA, USA<br>[redacted], ABCSG, Nussdorfer Platz 8, 1190 Wien, Austria<br>[redacted], ABCSG, Nussdorfer Platz 8, 1190 Wien, Austria<br>[redacted], ABCSG, Austria<br>[redacted], Genentech, South San Francisco, CA, USA<br>[redacted], Genentech, South San Francisco, CA, USA<br>[redacted] Spain<br>[redacted] Spain<br>[redacted], Genentech, South San Francisco, USA<br>[redacted], Belgium<br>[redacted] Belgium<br>[redacted], Spain<br>[redacted], SOLTI Breast Cancer Research Group, Diputació 256 4º1ª 08007 Barcelona, Spain<br>[redacted], Spain |

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2- NEGATIVE, EARLY STAGE BREAST CANCER** |
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38 |
| **VERSION NUMBER:** | 3 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | 110184 |
| **TEST PRODUCT:** | GDC-0032 |
| **PHASE:** | II |
| **INDICATION:** | Early stage breast cancer |
| **SPONSOR:** | Genentech, Inc. |

**Objectives**

**Efficacy Objectives**

The primary objective of this study is to evaluate the efficacy of letrozole plus GDC-0032 versus letrozole plus placebo in women with estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) early stage breast cancer, as measured by the following co-primary endpoints:

- Tumor overall objective response rate (ORR) by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in all enrolled patients and *PIK3CA* mutant (MT) patients
- Pathologic complete response (pCR) rate in breast and axilla (ypT0/Tis ypN0) by local evaluation in all enrolled patients and *PIK3CA* MT patients

The secondary efficacy objectives of this study are the following:

- Tumor objective response rate (ORR), assessed by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR ypT0/Tis ypN0) by local evaluation in *PIK3CA* wildtype (WT) patients

The following secondary objectives will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of locally assessed ORR *as measured by modified RECIST criteria (Appendix 3*) using the following methods:
  - Breast ultrasound
  - Clinical breast exam (i.e., palpation)
  - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery.

- Compare the centrally *derived,* preoperative endocrine prognostic index (PEPI) score upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo.
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment.
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

**Safety Objective**

The safety objective for this study is as follows:

- Evaluate the safety of letrozole plus GDC-0032 versus letrozole plus placebo

**Patient-Reported Outcome Objectives**

The patient-reported outcome (PRO) objectives for this study are as follows:

- Evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23)

**Exploratory Objectives**

The exploratory objectives for this study are as follows:

- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess whether biomarkers from tumor tissue or blood, including but not limited to somatic cancer associated mutations, PTEN expression, pro-survival pathways (such as PI3K/AKT, MAPK etc.), apoptotic markers, and levels of RNA and DNA expression are predictive of response
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to anti-tumor activity
- To assess concordance and percentage of *PIK3CA* mutation status from baseline biopsy and surgical specimen
- To assess emergence of resistance alleles from tumor tissue or blood
- To assess concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response
- To assess the pharmacokinetics and possible drug interaction between letrozole and GDC-0032 upon concomitant administration
- To assess the correlation of GDC-0032 drug levels and GDC-0032 related response (efficacy or adverse events [e.g., colitis, rash])
- To assess the influence of pharmacogenetic polymorphisms on GDC-0032 and/or letrozole on pharmacokinetics and response (either efficacy and/or adverse events)
- Compare the rates of breast-conserving surgery (BCS) and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo.

## Study Design

**Description of Study**

This is a two-arm, randomized, double-blind, multicenter, pre-operative study to evaluate the effect of combining letrozole and GDC-0032 versus letrozole and placebo in postmenopausal women with ER+/HER2- untreated, Stage I-III operable breast cancer whose primary tumors are $\geq$ 2 cm. Patients with cT4 or cN3 tumors are not eligible. Standard of care assessments/procedures (e.g., bilateral mammogram) performed within 28 days of Day 1 dosing do not need to be repeated for screening purposes.

All patients will undergo pretreatment tumor tissue acquisition (snap-frozen [optimal cutting temperature; OCT] and formalin-fixed paraffin-embedded cores [FFPE]). Two pretreatment FFPE core biopsies and one freshly frozen core biopsy must be obtained for all patients prior to beginning study drug treatment. Prior diagnostic FFPE core biopsies may be used for enrollment eligibility purposes. For the purpose of enrollment, ER, progesterone receptor (PR), and HER2 will be locally determined prior to beginning of study treatment. ER, PR, HER2, and

the percentage of Ki67-positive cells will also be centrally assessed, but the results do not have to be available prior to enrollment in the study. Remaining tissue will be retained for future translational studies. Pre-surgical sentinel lymph node biopsy (SLNB) is not allowed.

Patients will be randomized into one of the two treatment arms with a 1:1 randomization ratio. Letrozole at 2.5 mg will be dosed once daily plus either GDC-0032 at *4* mg *(two 2-mg tablets)* placebo on a 5 – days-on/ 2 – days-off schedule for a total of 16 weeks (see Figure 5). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

After confirmation of all the eligibility criteria, patients will be randomized to one of the treatment arms. A second biopsy will be performed on Day 15 (Week 3) for biomarker analyses. Biopsies should be performed at least 2 hours after GDC-0032 dose administration.

Randomization will be stratified according to 2 factors:

1. Tumor size (T1-T2 vs. T3)
2. Nodal status (cytologically positive vs. radiologically or cytologically negative)

The study will enroll approximately 330 patients at approximately 110 global sites.

At Weeks 1, 5, 9, 13, and 16 the primary breast tumor and axillary lymph nodes will be assessed by clinical breast examination (palpation and caliper measurement). Suspicion of progression based on clinical exam at any time should be further evaluated (Figure 6).

At Week 9, a breast ultrasound will be performed to ensure that there is no progressive disease and for the purpose of surgery planning. Suspicion of progressive disease on breast ultrasound should be confirmed by investigator-assessed breast MRI. Patients with primary disease not evaluable by ultrasound at baseline should be assessed by MRI at Week 9. Suspected progression in nodes should also be confirmed by fine needle aspiration (FNA) if these nodes had not been previously shown to be cytologically positive for cancer. Patients with progressive disease (as defined by modified RECIST, Appendix 3), can either proceed directly to surgery or be taken off of the study, according to the investigator's decision. If the patient goes off-study, every reasonable effort should be made to obtain a new biopsy prior to beginning another systemic treatment.

From Week 13, the patient will visit with the surgeon. The purpose of this visit is two-fold: tentative planning of the type of breast surgery to be performed (breast conservative vs. mastectomy) and scheduling the date for definitive surgery.

During Week 16, breast MRI will be done for the purpose of primary endpoint analysis. Clinical breast exam, breast ultrasound, and mammography will also be conducted prior to surgery for the purpose of the secondary endpoint analysis.

Blood sample for exploratory endpoint analysis will be collected *on Day 1 prior to dosing,* at Week *9*, and prior to surgery.

**Surgery**

Surgery will take place after at least 16 weeks of treatment, during Weeks 17 – 18. Surgery should be performed within 4 days after the last dose of GDC-0032, if possible, to best observe pharmacodynamic knockdown with GDC-0032 in the surgical specimen. Surgery may be delayed due to toxicity or other safety issues, upon discussion with the Medical Monitor (see Section 5.4.1) or recommendations from the Independent Data Monitoring Committee (IDMC; see below). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

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. Surgery specimens will be collected for histological examination to assess for pCR and for other endpoint analyses.

Following surgery, follow-up will proceed according to local standards of care. Adjuvant endocrine therapy and/or chemotherapy will be delivered as per the investigator's choice. Postoperative radiotherapy is required if BCS is performed. In the event of mastectomy, radiotherapy is to be administered according to local guidelines.

A postsurgery visit will be performed 4 weeks (+ 1 week) after surgery, and will mark the end of the study. Assessment of adverse events and general safety will be collected at this visit and the plan for future treatment will be recorded.

The patient should be evaluated at baseline and after Week 13 of treatment for planning the surgical procedure (BCS or mastectomy), and both *the planned and actual surgical treatment* should be documented in the electronic Case Report Form (eCRF).

The co-primary efficacy endpoint, pathological complete response (pCR–ypT0/is, ypN0) will be established via a local review following completion of neoadjuvant therapy and surgery.

Please refer to the pathology manual for further guidance of evaluation for pCR and directions for sending a copy of the pathology report.

A schedule of assessments is provided in Appendix 1.

An Independent Review Facility (IRF) will be used to determine the tumor ORR via MRI. IRF procedures are detailed in the IRF charter.

**Number of Patients**

The study will enroll approximately 330 patients at approximately 110 global sites.

**Target Population**

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF) prior to any study-specific procedure
- Female patients
- Postmenopausal status and age ≥ 18 years. Postmenopausal status is defined as follows:
  - Age ≥ 60 years or
  - Age < 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment or
  - Prior bilateral oophorectomy (≥ 28 days prior to Day 1 of treatment)
- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor ≥ 2 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 ≥ 2 cm and designated as the "target" lesion for all subsequent tumor evaluations.
  - Stage I to operable Stage III breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms).
- ER-positive and HER2-negative breast cancer, as per local laboratory or regional definition
- Breast cancer eligible for primary surgery
- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for *PIK3CA* mutation status by central histopathology laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Fasting glucose ≤ 125 mg/dL
- Adequate hematological, renal, and hepatic function, as follows:
  - Absolute neutrophil count ≥ 1500/μL
  - Platelets count ≥100,000/μL
  - Hemoglobin ≥ 9 g/dL
  - Serum bilirubin ≤ 1.5 × the upper limit of normal (ULN)
  - Patients with known Gilbert's disease who have serum bilirubin ≤ 3 × ULN may be enrolled

- Aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase $\leq 1.5 \times$ ULN Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation:

  $(140 - \text{age}) \times (\text{weight in kg}) \times (0.85)$
  $72 \times (\text{serum creatinine in mg/dL})$
- International normalized ratio (INR) $< 1.5 \times$ ULN and activated partial thromboplastin time (aPTT) $< 1.5 \times$ ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2–3 is required. If anticoagulation is required for a prosthetic heart valve, then INR should be between 2.5–3.5.
- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Ability and willingness to comply with study visits, treatment, testing, and to comply with the protocol, in the investigator's judgment

Exclusion Criteria

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

- Any prior treatment for primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer
- 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 sentinel lymph node biopsy prior to study treatment
- Patients for whom upfront chemotherapy is clinically judged appropriate as optimal neoadjuvant treatment
- Patients for whom immediate surgery is indicated
- Type 1 or 2 diabetes requiring antihyperglycemic medication
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteric absorption
- History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis)
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF) $> 470$ msec
- DLCO $< 60\%$ of the predicted values (see Appendix 7 for calculations)
- Clinically significant (i.e., active) cardiovascular disease, uncontrolled hypertension, unstable angina, history of myocardial infarction, cardiac failure class II-IV (New York Heart Association, Appendix 5), or any other that in the judgment of the investigator could jeopardize patient safety or study outcomes
- 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
- Active infection requiring intravenous (IV) antibiotics
- Patients requiring any daily supplemental oxygen
- Clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis
- Known human immunodeficiency virus (HIV) infection
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications
- Significant traumatic injury within 3 weeks prior to initiation of study treatment
- Major surgical procedure within 4 weeks prior to initiation of study treatment
- Inability to comply with study and follow-up procedures
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

**Concomitant 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 7 days prior to screening to the study completion/discontinuation visit.

GDC-0032 was metabolized primarily by CYP3A4 in HLM and appeared to be a weak time dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low-to-moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC 0032 may be administered concomitantly with CYP3A4 substrates without the risk of a pharmacokinetic drug-drug interaction (DDI).

**Prohibited Therapy**

Prohibited therapy is as follows:

- **Anti-cancer therapy:** No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than letrozole permitted in this protocol) will be allowed.
- **Hormone replacement therapy**, **topical estrogens (including any intra-vaginal preparations), hormonal contraception, megestrol acetate, and selective estrogen-receptor modulators used with prophylactic intent**: If a patient is receiving these at the moment of registration, treatment should be discontinued prior to randomization.
- **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.
- **Potent CYP3A4 inhibitors:** Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole and itraconazole) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If a strong CYP3A4 inhibitor is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.

- **Potent CYP3A4 inducers:** Concomitant use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, phenobarbital) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to induce CYP3A4. If a strong CYP3A4 inducer is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.

**Length of Study**

The total duration of the study is expected to be approximately 24 months for enrollment, plus 5.5 months after last patient in.

**End of Study**

The end of the study is defined as the date when the last patient has her postsurgery visit.

**Outcome Measures**

**Co-Primary Efficacy Outcome Measures**

The co-primary efficacy outcome measures for this study are as follows:

- Tumor ORR via centrally assessed breast MRI *(centrally assessed)* via modified RECIST (Appendix 3) in all enrolled patients and *PIK3CA* MT patients
- pCR rate in breast and axilla (total pCR) as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system (Appendix 6) by local evaluation in all enrolled patients and *PIK3CA* MT patients

**Secondary Efficacy Outcome Measures**

The secondary efficacy outcome measures for this study are as follows:

- Tumor ORR, assessed by centrally assessed breast MRI via modified RECIST (Appendix 3) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR) by local evaluation in *PIK3CA* WT patients

The following secondary outcome measures will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of ORR, as measured by modified RECIST criteria (Appendix 3) using the following methods:
  - Breast ultrasound
  - Clinical breast exam (i.e., palpation)
  - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally *derived* PEPI score upon treatment with letrozole plus GDC-0032 with letrozole plus placebo
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) yoT0/is, ypNX (breast pCR)

**Safety Outcome Measures**

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0)
- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Serious adverse events
- Protocol-defined adverse events of special interest
- Clinically significant changes in vital signs and in clinical laboratory results during the adverse event reporting period (see Section 5.3.1)

**Patient-Reported Outcome Measures**

The PRO outcome measures for this study are as follows:

- HRQoL, including side-effects of therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems), and patient functioning as measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ–C30) and the modified breast cancer module QLQ–BR23

**Exploratory Outcome Measures**

The exploratory outcome measures for this study are as follows:

- ORR, pCR rate, and PEPI scores according to the decrease in Ki67 after 2 weeks of letrozole plus GDC-0032 and letrozole plus placebo.
- Expression of biomarkers before, during, and after therapy. These include, but are not limited to, the following:
  - PI3K pathway aberrations
  - Gene signatures, including intrinsic subtyping and PI3K pathway activity
  - Protein and phospho-protein markers and combinations
  - Mutations within cancer-associated genes
  - Copy number alterations in cancer-related genes
  - Plasma-based protein biomarkers
  - Circulating tumor DNA (ctDNA)
- Compare the rates of BCS and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo
- The relationship between GDC-0032 concentration and tumor response and/or drug safety response
- Letrozole concentrations with and without administration of GDC-0032
- The relationship between pharmacogenetic differences in drug metabolizing enzymes and transporters and other patient-specific covariates with PK of GDC-0032 or letrozole and/or drug response
- Changes from baseline to surgery in the apparent diffusion coefficient (ADC), a marker of tumor cellularity derived from diffusion-weighted MRI
- Concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response

**Investigational Medicinal Products**

Study treatment is neoadjuvant (pre-operative) therapy.

**Test Product**

The test product for this study is GDC-0032. Patients will receive an oral, daily dose of 4 mg *(two 2-mg tablets)* GDC-0032 or placebo on a schedule of 5 days on/2 days off for a maximum of 16 weeks. Patients will take GDC-0032 at the same time of day ± 2 hours, unless otherwise instructed. Patients will be instructed as to the number of tablets to take.

Information on the formulation, packaging, handling, and administration of GDC-0032 are provided in the GDC-0032 Investigator's Brochure.

**Non-Investigational Medicinal Products**

**Letrozole**

Letrozole is a marketed product that is approved in the European Union and the United States for the treatment of hormone receptor-positive breast cancer. Based upon the different mechanisms of action of GDC-0032 and the well-established safety profile of letrozole, there are no expected overlapping, significant toxicities between letrozole and GDC-0032.

Patients will receive an oral, daily dose of 2.5 mg letrozole for 16 weeks (or until time of surgery at the investigator's discretion).

## Statistical Methods

### Primary Analysis

This study is designed for testing the effect of GDC-0032 on the two co-primary endpoints in all enrolled patients and in the *PIK3CA* MT patients and plans to enroll 330 patients in total. Assuming the *PIK3CA* mutation status will not be available (unknown) for approximately 10% of the patients and the prevalence of *PIK3CA* mutant is 40%, there will be approximately 120 patients in the *PIK3CA* MT cohort.

Given that the *PIK3CA* mutation status is not a stratification factor for randomization, there might be a possible imbalance between treatment arms within the *PIK3CA* MT cohort, which may reduce the statistical power in this cohort. To ensure the study provides sufficient statistical power even when the treatment assignment is imbalanced, the sample size was calculated based on a conservative scenario by assuming that the treatment assignment imbalance in *PIK3CA* MT is 40% vs. 60%. The sample size was calculated based on a $chi^2$-test using continuity correction (Ury and Fleiss 1980).

To control an overall two-sided, family-wise error rate under 20%, we use a two-sided significance level of 16% and 4% for the co-primary endpoints MRI ORR, and pCR, respectively.

Assuming 10% of the patients are unevaluable for the MRI ORR, approximately 300 enrolled patients and 108 patients in the *PIK3CA* MT cohort will be evaluable for analyses. This sample size allows us to detect an absolute percentage increase of 24% in MRI ORR rate in the GDC-0032 plus letrozole arm (64%) versus the letrozole-only arm (40%; Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at 80% power and 16% two-sided significance level. The minimal detectable difference for ORR is approximately 15%.

Assuming that all patients are evaluable for pCR (i.e., approximately 330 enrolled patients and 120 in the *PIK3CA* MT cohort), this sample size provides 80% power to detect an absolute percentage increase of 18% in pCR in the GDC-0032 plus letrozole arm (19%) versus the letrozole-only arm (1%, Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at the 4% two-sided significance level. The minimal detectable difference for pCR rate is approximately 13%.

If the prevalence of the *PIK3CA* mutation is lower than assumed, if there is more substantial treatment assignment imbalance in the *PIK3CA* MT cohort than assumed, or there is an increased number of unevaluable patients for the MRI ORR, the sample size may be increased to obtain the level of power at 80%, and the enrollment may be limited to patients with *PIK3CA* MT.

### Secondary Analysis

The secondary efficacy endpoints for this study are as follows:

- Tumor ORR after completion of study treatment, assessed by modified RECIST criteria by breast MRI *(centrally assessed)* in *PIK3CA* WT patients.
- Rate of pCR in breast and axilla (total pCR) after completion of study drug in *PIK3CA* WT patients.

These endpoint measures will be summarized by treatment arm and will be analyzed analogue to the primary efficacy endpoint.

The following secondary efficacy endpoints will be performed in all enrolled patients and separated by *PIK3CA* mutation status *(centrally assessed)*:

- ORR *using modified RECIST criteria by the following methods:* by clinical breast examination, mammography and breast ultrasound
- Ki67 values at baseline, Week 3, and surgery (centrally assessed)
- Change in Ki67 from baseline to Week 3; baseline to surgery, and Week 3 to surgery (centrally assessed)
- PEPI score (centrally *derived*)
- Change in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluation of different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

These endpoint measures will be summarized by treatment arm and will be compared between the two treatment arms within each population based on appropriate statistical analyses: ORR will be compared using a Cochrane Mantel-Haenszel test, stratified by tumor size and nodal status; PEPI, Ki67, and tumor volume change will be compared by regression analyses, adjusted for tumor size and nodal status. All secondary endpoints will be tested at a two-sided type I error of 5%.

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

**Determination of Sample Size**

Please refer to the primary analysis in the Statistical Methods section.

**Interim Analyses**

An Independent Data Monitoring Committee (IDMC) will monitor accumulating patient safety data at a minimum of once every 6 months until the last patient has completed study treatment. Additional details (e.g., IDMC members, communication, affiliations) will be provided in the IDMC charter.

The IDMC will conduct interim analyses to review the unblinded safety data after the first 20 patients have either 1) finished the 30-day follow-up visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery). The IDMC will create and review unblinded, pooled summaries of the safety and available PK summaries (all interim analyses). While this review is being conducted, patient accrual into the study will continue. The Medical Monitor may also request additional safety analysis and may call for additional meetings of the IDMC to review ongoing safety data.

The IDMC will share results from interim safety analyses with the study team. The study team will share interim safety results with study investigators as needed for the conduct of the study and the safety of the patients. Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections. All available information of all enrolled patients with all available assessments at the respective timepoint will be included in the interim analyses.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ABCSG | Austrian Breast and Colorectal Cancer Study Group |
| ADC | apparent diffusion coefficient |
| AE | adverse events |
| AI | aromatase inhibitors |
| ALT | alanine transaminase |
| aPTT | activated partial thromboplastin time |
| ASCO-CAP | American Society of Clinical Oncology-College of American Pathologists |
| AST | aspartate aminotransferase |
| *AUC* | *area under the curve* |
| $AUC_{0-24}$ | area under the concentration–time curve from 0 to 24 hours |
| $AUC_{0-inf}$ | *area under the concentration–time curve from 0 to infinity* |
| BCS | breast conserving surgery |
| BIG | Breast International Group |
| BUN | blood urea nitrogen |
| CD | compact disc |
| CI | confidence interval |
| $C_{max}$ | maximum plasma concentration observed |
| $C_{min}$ | minimum concentration under steady-state conditions within a dosing interval |
| cPR | confirmed partial responses |
| CRA | clinical research associate |
| CRO | contract research organization |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating tumor DNA |
| CTNeoBC | Collaborative Trials in Neoadjuvant Breast Cancer |
| DCR | data clarification request |
| DDI | drug-drug interaction |
| DLCO | diffusion capacity of the lung for carbon monoxide |
| DLT | dose-limiting toxicity |
| DMP | data management plan |
| DXA | dual-energy X-ray absorptiometry |
| DVD | digital video disk |
| EC | Ethics Committee |

| Abbreviation | Definition |
|---|---|
| $EC_{50}$ | 50% effective concentration |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EGFR | epidermal growth factor receptor |
| ELISA | enzyme-linked immunosorbent assay |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ER+ | estrogen receptor-positive |
| E.U. | European Union |
| FFPE | formalin-fixed paraffin-embedded |
| FDA | Food and Drug Administration |
| FNA | fine needle aspiration |
| FSH | follicle stimulating hormone |
| GCP | good clinical practice |
| HbA1c | Glycosylated hemoglobin |
| HDL | high-density lipoprotein |
| HDPE | high-density polyethylene |
| HER2 | human epidermal growth factor receptor 2 |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HLA | human leukocyte antigen |
| HLM | human liver microsomes |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| *IGF-1R* | *insulin-like growth factor-1 receptor* |
| IHC | immunohistochemistry |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (application) |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IRF | Independent Review Facility |
| ISH | in situ hybridization |

| Abbreviation | Definition |
|---|---|
| ITT | intent to treat |
| IV | intravenous |
| IxRS | interactive voice or web-based response system |
| LDL | low-density lipoprotein |
| LPLV | last patient, last visit |
| MAPK | mitogen-activated protein kinase |
| MDD | minimum detected difference |
| MP | monitoring plan |
| MRI | magnetic resonance imaging |
| MT | mutant |
| MTD | maximum tolerated dose |
| mTOR | mammalian target of rapamycin |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NGS | next generation sequencing |
| NSCLC | non – small-cell lung cancer |
| nu/nu | immunocompromised nune (mice) |
| OCT | Optimal cutting temperature |
| ORR | objective response rate |
| pAKT | phosphorylated form of AKT |
| pCR | pathologic complete response |
| PD | progressive disease |
| PEPI | preoperative endocrine prognostic index |
| PFS | progression-free survival |
| PFT | pulmonary function test |
| PI3K | phosphatidylinositol-3-kinase |
| PIP2 | phosphatidylinositol-4,5-bisphosphate |
| PIP3 | phosphatidylinositol 3,4,5 trisphosphate |
| PO | oral |
| PR | progesterone receptor |
| PRO | patient-reported outcome |
| PTEN | phosphatase tensin homolog |
| QD | once daily |
| QLQ-BR23 | Quality of Life Questionnaire Breast Cancer Module |
| QLQ-C30 | Quality of Life Questionnaire Core 30 |
| QTcF | QT interval corrected using Fridericia's formula |
| RBC | red blood cell |

| Abbreviation | Definition |
|---|---|
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RFS | relapse-free survival |
| RPPA | reverse phase protein array |
| RT-PCR | real-time polymerase chain reaction |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SDV | source data verification |
| SLNB | sentinel lymph node biopsy |
| SOLTI | Spanish Breast Cancer Research Group |
| SOP | standard operating procedure |
| SmPC | summary of product characteristics |
| $t_{1/2}$ | terminal half-life |
| TGI | tumor growth inhibition |
| ULN | upper limit of normal |
| U.S. | United States |
| WBC | white blood cell |
| WT | wildtype |

# 1. BACKGROUND

## 1.1 BACKGROUND ON THE PHOSPHATIDYLINOSITOL-3-KINASE PATHWAY

Phosphatidylinositol-3-kinase (PI3K) is a lipid kinase involved in tumor cell proliferation, survival, and migration upon activation by growth factor receptors and integrins. PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3) (Cantley 2002), a second messenger involved in the phosphorylation of AKT and associated proteins in the AKT-mammalian target of rapamycin (mTOR) pathway (Guertin and Sabatini 2007). Activating and transforming mutations, as well as amplification, in the p110$\alpha$ subunit of PI3K are commonly found in solid and hematological tumors (Li et al. 1997). In addition, the PI3K-AKT pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling, the loss of the phosphatase tensin homolog (PTEN) *and Inositol Polyphosphate 4-phosphatase type II (INPP4B)*, or RAS mutations (Shayesteh et al. 1999; Cantley 2002; Massion et al. 2004; Wu et al. 2005).

## 1.2 BACKGROUND ON ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER

Breast cancer is the most frequently diagnosed cancer worldwide and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of total cancer deaths (Jemal et al. 2011). As a large proportion of breast cancer cases, especially in developed countries, are now diagnosed in early stages, they are amenable to cure with a stage-appropriate combination of surgery, systemic therapy (chemotherapy and/or hormonal therapy), and radiotherapy.

Estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer accounts for about 60%–70% of all breast cancers. However, not all ER+ breast cancers respond optimally to endocrine therapy (Davies et al. 2011). There are several mechanisms that can lead to primary and/or secondary hormonal resistance in ER+ breast cancer: decrease of ER expression, loss of ER expression, or upregulation of growth factor signaling pathways, such as the epidermal growth factor receptor (EGFR)/HER2, the mitogen-activated protein kinase (MAPK), or the PI3K/AKT/mTOR pathways (Johnston 2009).

In the setting of ER+/HER2-negative breast cancer, the PI3K/AKT/mTOR pathway plays an important role in mediating hormonal resistance and is a viable therapeutic target to explore (Miller et al. 2010).

## 1.3 BACKGROUND ON THE PI3K/AKT/MTOR PATHWAY AND BREAST CANCER

Genes in the PI3K/AKT/mTOR signaling pathway are frequently mutated or amplified in breast cancer, especially in the ER+ subtype (Cancer Genome Atlas Network 2012). Molecular alterations of the PI3K/AKT/mTOR pathway include the following: (1) Mutations or amplifications in *PIK3CA*, the gene encoding the alpha catalytic subunit of PI3K (p110$\alpha$) (Saal et al. 2005; Wu et al. 2005); (2) Alterations in the tumor suppressor gene PTEN, either by loss of protein expression (PTEN null), inactivation mutations and/or epigenetic deregulation through promoter hypermethylation (García et al. 2004); (3) PDKP1 amplification and/or overexpression (Brugge et al. 2007); (4) AKT1 somatic gain of function mutations (Stemke-Hale et al. 2008) and AKT2 amplifications (Bellacosa et al. 1995). Overall, it is estimated that up to 70% of breast cancers can have some form of molecular aberration of the PI3K/AKT/mTOR pathway (CGAN 2012).

## 1.4 BACKGROUND ON REVERSING HORMONAL RESISTANCE BY INHIBITING THE PI3K/MTOR/AKT PATHWAY

In the setting of ER+ breast cancer, PI3K seems to play an important role in mediating hormonal resistance and $is$ a viable therapeutic target. Hyperactivation of this signaling pathway was proved to promote both *de novo* and acquired resistance to hormone therapy in ER+ breast cancer cell lines and xenograft models (Sabnis et al. 2007), and simultaneous blocking of the PI3K/AKT/mTOR pathway with everolimus and the ER pathway with letrozole enhances antitumor activity of either agent alone (Boulay et al. 2005). Importantly, a baseline protein signature of PI3K activation was found to be predictive of a poor prognosis after adjuvant endocrine therapy (Miller et al. 2010).

In the clinical setting, impressive results of the combination of exemestane and everolimus, an mTOR inhibitor, were reported in the BOLERO-2 trial (Baselga et al. 2009). This trial compared everolimus and exemestane with placebo and exemestane in 724 postmenopausal patients with ER+ advanced breast cancer who had experienced recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting and/or in advanced disease. Median progression-free survival (PFS) in the everolimus group was 6.9 months, as compared to 2.8 months in the placebo group. Hazard ratio (HR) for progression or death was 0.43, with a 95% confidence interval (CI) of $0.35-0.54$ ($p<0.001$), as per the investigator's assessment, and the magnitude of the effect was even greater as per central assessment (HR, 0.36, 95% CI, $0.27-0.47$; $p<0.001$). In the open-label Phase II TAMRAD trial, patients with aromatase inhibitors (AI) resistant metastatic breast cancer received tamoxifen plus everolimus or tamoxifen alone (Bachelot et al. 2012). The 6-month clinical benefit rate was 61% (95% CI, $47\%-74\%$) with tamoxifen plus everolimus and 42% (95% CI, $29\%-56\%$) with tamoxifen alone. Time to progression increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus everolimus, corresponding to a 46% reduction in risk of progression with the combination

(HR, 0.54; 95% CI, 0.36 – 0.81). Risk of death was reduced by 55% with tamoxifen plus everolimus versus tamoxifen alone (HR, 0.45; 95% CI, 0.24 – 0.81).

In the neoadjuvant setting, combination of letrozole and everolimus also resulted in improved responses over letrozole alone in patients with ER+ breast cancer (Baselga et al. 2009). In this study, 270 postmenopausal patients with operable ER+ breast cancer were randomly assigned to receive 4 months of neoadjuvant treatment with letrozole and either everolimus or placebo. The primary endpoint of the trial, clinical response by palpation, was higher in the everolimus arm than in the control arm (68.1% vs. 59.1%, $p = 0.062$), a statistically significant result (one-sided, $\alpha = 0.1$ level).

An important finding in trials with mTOR-targeting drugs like everolimus is that they produce a pharmacodynamic paradox: while inhibiting mTOR, they lead to an upregulation of the phosphorylated form of AKT (pAKT), resulting in feedback PI3K/AKT/mTOR pathway activation (Tabernero et al. 2009). This finding suggests that alternative pharmacologic strategies to effectively shut down the pathway upstream of AKT should be pursued. One of these strategies is inhibiting the PI3K/AKT/mTOR pathway at the level of PI3K.

## 1.5 BACKGROUND ON NEOADJUVANT THERAPY IN 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 and Smith 2003; Scholl et al. 1994; Semiglazov et al. 2004; Fisher et al. 2012; Wolff and Davidson 2000). The randomized studies evaluating neoadjuvant therapy as well as meta-analyses of these studies have shown that neoadjuvant therapy can improve breast conservation rates, decreasing the number of women obligated to undergo mastectomy (Mieog et al. 2007; Fisher et al. 2012). 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 $distant$ disease recurrence based upon the timing of the systemic therapy (Mauri et al. 2005). The concept of neoadjuvant therapy is now well established and a standard treatment option for patients with early breast cancer. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis was recently conducted evaluating over 12,000 patients treated with neoadjuvant chemotherapy as part of clinical trials (Cortazar et al. 201$4$). The results of this meta-analysis confirmed an association of pathologic complete response [pCR] with favorable long-term outcomes in high-risk populations (i.e., HER2-positive, high-grade hormone receptor positive and triple negative subtypes), although the magnitude of pCR improvement predictive of the long-term survival benefits could not be determined. In September 2013, the Food and Drug Administration (FDA) granted accelerated approval of Perjeta as part of a complete treatment regimen for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer in the neoadjuvant setting.

## 1.6 BACKGROUND ON GDC-0032

GDC-0032 is a potent selective inhibitor of Class I PI3K alpha, delta, and gamma isoforms, with 30-fold less potent inhibition of the beta isoform that is being developed as a therapy for human cancers. Nonclinical studies with GDC-0032 demonstrate that GDC-0032 inhibits proliferation of p110$\alpha$-mutant breast cell lines, inhibits tumor growth in human breast xenograft models harboring *PIK3CA* mutations, and results in a substantial reduction of PI3K pathway markers, including pAkt, pPRAS40, and pS6.

GDC-0032 has demonstrated activity in nonclinical models of *PIK3CA*-mutant breast tumors in vivo as a single agent and in combination with standard of care (e.g., paclitaxel or docetaxel) or endocrine therapies (e.g., letrozole or fulvestrant). GDC-0032 has a favorable in vitro and nonclinical in vivo absorption, distribution, metabolism, and elimination profile that has characteristics consistent with a compound that can be delivered orally to achieve clinical exposure similar to the nonclinical efficacy findings described herein. Additional studies, including 16-week toxicity studies in rats and dogs, phototoxicity studies, and an embryo-fetal development study, support the Phase II neoadjuvant trial with GDC-0032 in combination with endocrine therapy.

In vitro, single-agent GDC-0032 potency is also observed in cell lines that do not harbor *PIK3CA* mutations (Figure 1). In in vitro combination studies, the aromatase-expressing breast cancer cell line (MCF7X2.3.ARO) showed positive combination effects between GDC-0032 and endocrine therapies (see Figure 2). In this cell line, GDC-0032 alone caused growth inhibition (50% effective concentration [$EC_{50}$] = 95 nM). Effects on growth were also observed with letrozole and fulvestrant. Combined treatment of cells with GDC-0032 and letrozole caused dose-dependent inhibition of cell viability at lower concentrations of either GDC-0032 or letrozole resulting in enhanced activity for the combination. In addition, combination activity was demonstrated in the *PIK3CA* wild-type (WT) cell line ZR75-1 when GDC-0032 was added to either fulvestrant or tamoxifen endocrine therapies (combination with letrozole not available in this cell line). However, in vivo data in a *PIK3CA* WT model are not available, because these cell lines do not grow as xenografts.

**Figure 1 GDC-0032 Potency in Non-*PIK3CA* Mutant Breast Cancer Cell Lines**

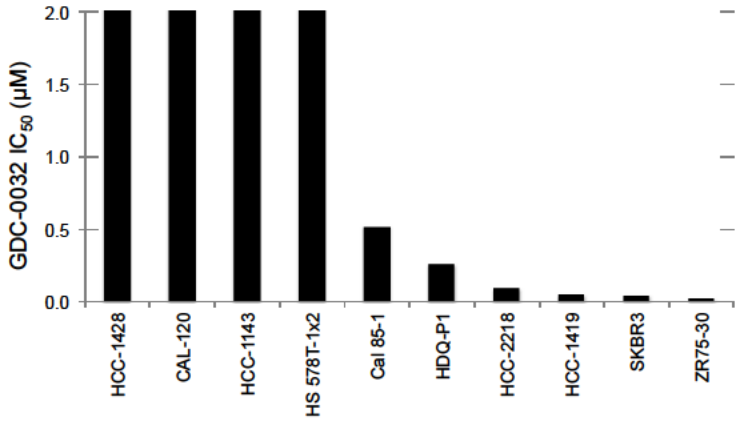
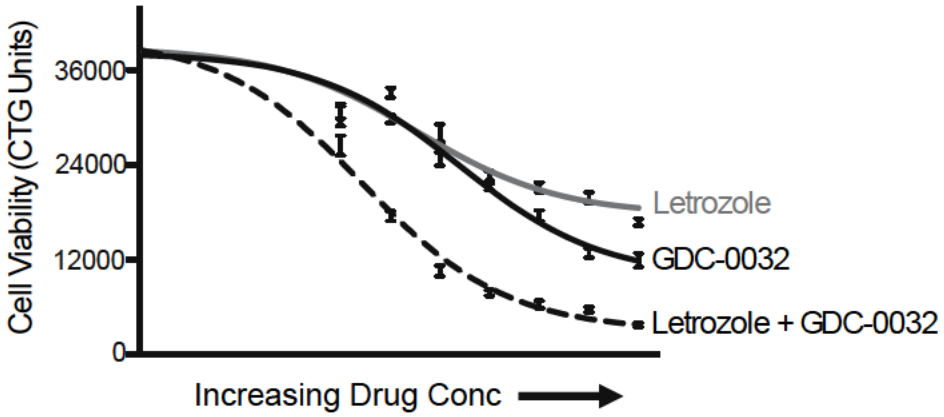


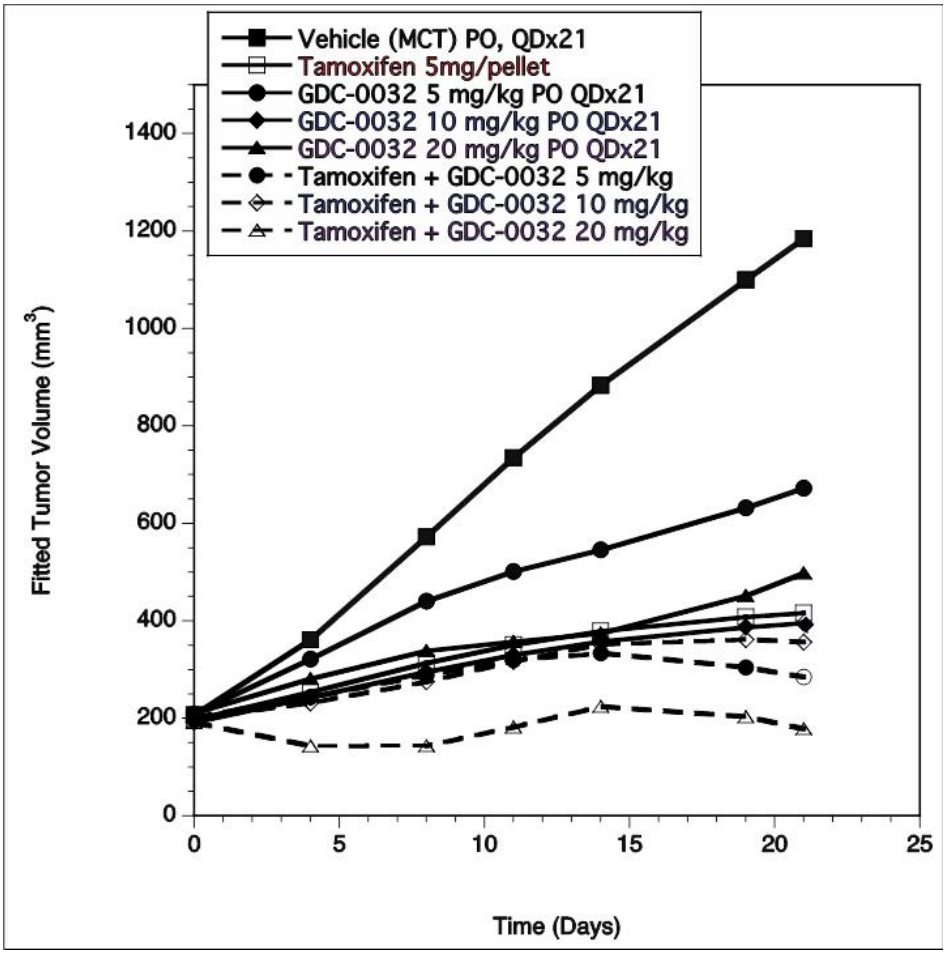

**Figure 2 Combination Effects between Letrozole and GDC-0032 in the Aromatase-Expressing MCF7.2x3 Breast Cancer Cell Line**




Conc = concentration.
MCF7X2.3.ARO (aromatase-expressing MCF7 cells) are sensitive to GDC-0032 in combination with endocrine therapies. Effects on viability are determined after 96 hours in culture.

Enhanced efficacy was demonstrated in combination with tamoxifen, another endocrine therapy used in the treatment of hormone receptor-positive breast cancer. In this human MCF7-neo/HER2 (*PIK3CA* mutant [MT]) breast cancer xenograft model in immunocompromised nude (nu/nu) mice, administration of GDC-0032 at all doses tested (5, 10, or 20 mg/kg) in combination with tamoxifen (5-mg/pellet) resulted in greater efficacy (shown as a percentage of tumor growth inhibition [TGI]: 82% TGI, 80% TGI, and 102% TGI, respectively) compared to tamoxifen alone (73% TGI) or GDC-0032 as a single agent (71% TGI at 20 mg/kg) (see Figure 3). All combinations were well tolerated with no increase in mortality and no greater body weight loss than single agents alone.

**Figure 3 Efficacy of Tamoxifen in Combination with GDC-0032 in MCF7-Neo/Her2 Estrogen Receptor-Positive Mouse Xenografts**




QD = once daily; PO = oral gavage.

Vehicle was MCT (0.5% methycellulose/0.2% Tween-80).

Tamoxifen pellets (5 mg/pellet, 60-day release) were implanted on Day 0 of dosing (8 days post tumor implantation). Tumor volumes after QD oral administration of GDC-0032 for 21 days are depicted by dose group.

Please refer to the GDC-0032 Investigator's Brochure for additional nonclinical data for GDC-0032 supporting this clinical trial.

### 1.6.1 Toxicology

Please refer to the GDC-0032 Investigator's Brochure for details on the toxicology program to support this clinical trial.

## 1.7 SUMMARY OF CLINICAL DATA FOR GDC-0032

### 1.7.1 Clinical Safety Data with GDC-0032

As of 5 July 2013, a total of 144 patients have been treated with GDC-0032 *capsules, in the Phase I/II PMT4979g study,* either as single agent (*n* =90, 63%) or in combination with endocrine therapy (*n* =54, 37%).

As of 5 July 2013, enrollment into the dose-escalation stage of Study PMT4979g had been completed with 34 patients enrolled at *GDC-0032* doses *ranging from* 3 to 16 mg daily. GDC-0032 was well tolerated in the first three cohorts (3, 5, and 8 mg), with no patients experiencing a dose-limiting toxicity (DLT). At the 16-mg dose level, 2 of the 11 safety-evaluable patients experienced a DLT (Grade 4 hyperglycemia and Grade 3 fatigue). At the 12-mg dose level, 1 of the 10 safety-evaluable patients experienced a DLT of Grade 3 acute renal failure. Although the single-agent GDC-0032 maximum tolerated dose (MTD) was not exceeded at the 16-mg dose level, the recommended GDC-0032 dose and schedule for the single-agent expansion cohorts is 9 mg daily on the basis of long-term safety data through multiple treatment cycles. As of the cutoff date, a total of 53 patients *had* been enrolled in the 9-mg daily dosing expansion cohorts.

As of 5 July 2013, adverse events *of any grade* that occurred in ≥10% of the 87 patients treated with daily single-agent GDC-0032 *capsules* and were *investigator*-assessed as related to GDC-0032 were as follows: diarrhea (47%), hyperglycemia (38%), nausea (36%), fatigue (*35*%), decreased appetite (31%), rash (25%), stomatitis (13%), vomiting (13%), and mucosal inflammation (*12*%). Grade 3 and 4 adverse events *assessed by the investigator as GDC-0032 related* included hyperglycemia (*12*%), colitis (*6%), rash (*5%), *diarrhea (3%), fatigue (3%),* pneumonitis (3%)*, pruritus (2%), stomatitis (2%),* increased *alanine* aminotransferase levels (1%), anemia (1%), increase in blood creatinine (1%), *exfoliative rash* (1%), hypokalemia (1%), hypophosphatemia (1*%), lung infection (1*%), pneumonia (1*%), erythematous rash (1%), generalized rash (1%), maculopapular rash (1%) and skin exfoliation (1*%), and *acute renal failure* (1%).

As of 5 July 2013, a total of 27 patients have been enrolled in the expansion cohort of GDC-0032 at dose levels of 6 and 9 mg daily (19 patients at 6 mg, and 8 patients at 9 mg) daily in combination with letrozole (Cohort E). No DLTs were observed at either dose level. Adverse events *of any grade and assessed by the investigator as drug related* that occurred in ≥ 10% of the 27 safety-evaluable patients assessed as related to GDC-0032 were diarrhea (67%), fatigue (30%), nausea (30%), *rash (30%),* decreased appetite (26%), hyperglycemia (26%), stomatitis (26%), dysgeusia (22%), mucosal inflammation (*19*%), asthenia (15%), pruritus (15%), vomiting (15%), *and* dry mouth (11%). Grade 3 and 4 adverse events *assessed by the investigator as GDC-0032 related include* diarrhea (11%), mucosal inflammation (7%), increased amylase *(4%), hyperglycemia (4*%), increased aspartate aminotransferase (AST) *(4%), stomatitis* (3.7%), increased *blood* alkaline phosphate *(4*%), fatigue (*4*%), increased

gamma-glutamyltransferase in the blood (4%), hypokalemia (4%), increased lipase in the blood, (4%), and papilloedema (4%).

As of 5 July 2013, a total of 27 patients have been enrolled in the expansion cohort of GDC-0032 at dose levels of 6 and 9 mg daily (21 patients at 6 mg and 6 patients at 9 mg) in combination with fulvestrant (Cohort F). No DLTs were observed at either dose level. One patient has been enrolled in the Phase II part of the study with 6 mg GDC-0032 in combination with fulvestrant. Adverse events *assessed by the investigator as GDC-0032 related and of any grade* that occurred in ≥ 10% of the 27 patients and were assessed as related to GDC-0032 were diarrhea (48%), hyperglycemia (33%), nausea (33%), decreased appetite (26%), fatigue (26%), rash (26%), stomatitis (22%), asthenia (19%), muscle spasms (15%), vomiting (15%), dysgeusia (11%), gastroesophageal reflux disease (11%) and mucosal inflammation (11%). Grade 3 and 4 adverse events *assessed by the investigator as related to GDC-0032* included hyperglycemia (15%), diarrhea (7%), dyspnea (4%), flank pain (4%), hyponatremia (4%), neutropenia (4%), rash (4%) and vomiting (4%).

Please refer to the GDC-0032 Investigator's Brochure for additional information.

#### 1.7.1.1 Preliminary Pharmacokinetics

Pharmacokinetic (PK) data are available from 34 patients treated with GDC-0032 at 3, 5, 8, 12, and 16 mg in the ongoing Phase I/II clinical trial (Study PMT4979g). The cohort mean apparent clearance and the terminal half-life ($t_{1/2}$) following a single, oral dose of GDC-0032 had a range of 4.77–9.17 L/hour and 36.7–43.8 hours, respectively. Following daily oral dosing for 8 days, there was a 2- to 4-fold accumulation of GDC-0032. The pharmacokinetics of GDC-0032 appears to be dose linear and time-independent. Preliminary PK data from Cohort E suggest there is no drug-drug interaction (DDI) between letrozole plus GDC-0032. Mean plasma exposure of letrozole when given in combination with GDC-0032 (maximum concentration observed [$C_{max}$] = 0.407 μM and area under the concentration–time curve from 0 to 24 hours [$AUC_{0-24}$] = 8.01 μM*hr) was comparable with the historical single-agent exposure ($C_{max}$ = 0.495 μM and $AUC_{0-24}$ = 10.1 μM*hr) (Awada et al. 2008). Similarly, plasma concentrations of GDC-0032, when given in combination with letrozole, were within the range predicted by the population PK model. Therefore, letrozole plus GDC-0032 can be co-administered without the risk of a DDI.

GDC-0032 was metabolized primarily by CYP3A4 in human liver microsomes (HLMs) and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low to moderate potential to induce CYP3A4, preliminary data from the Phase I/II study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a PK DDI.

*Preliminary data from a healthy volunteer study showed that the 3-mg GDC-0032 tablet produces an estimated geometric mean ratio (90% CI) of 196% (177.1 –217.0) for $C_{max}$ and 152.2% (141.9 –163.2) for AUC time 0 to infinity ($AUC_{0\text{-}inf}$) when compared with the 3-mg Phase I capsule. For this reason, a new 2-mg tablet has been formulated to deliver GDC-0032 exposure similar to the 3-mg capsule formulation.*

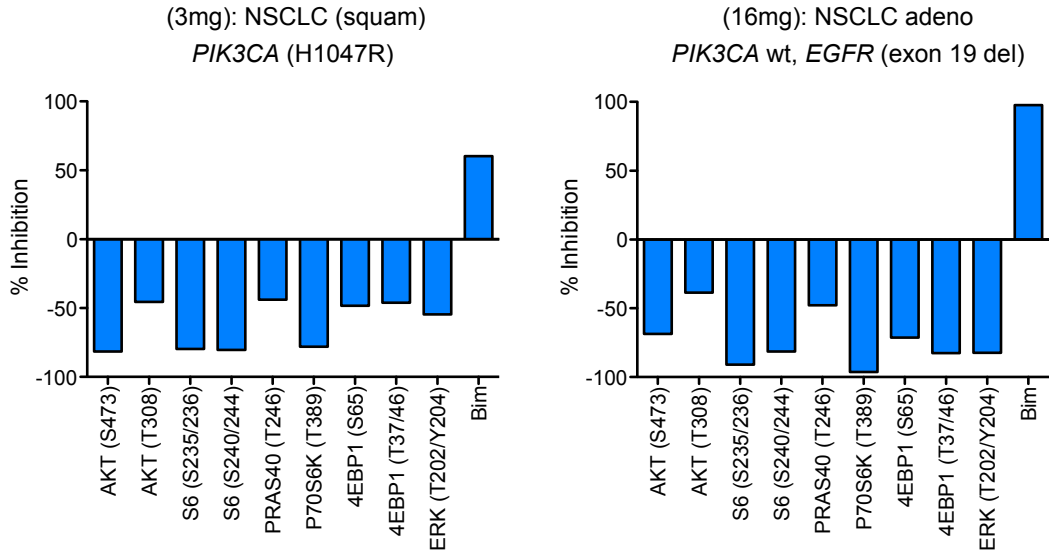
*The drug exposure (AUC) for GDC-0032 in a healthy volunteer study was minimally affected by the consumption of a high-fat meal. Therefore, GDC-0032 may be taken without regard to the timing of the administration of food.*

For additional details, refer to the GDC-0032 Investigator's Brochure.

### 1.7.1.2 Preliminary Pharmacodynamics

Paired tumor biopsies were obtained from both *PIK3CA* MT and *PIK3CA* WT non-small cell lung cancer (NSCLC) patients treated at either the 3-mg or 16-mg GDC-0032 dose level, respectively, at screening (pretreatment biopsy) and during Cycle 1 in Study PMT4979g (on-treatment biopsy). Inhibition of PI3K pathway markers, including decreases of >60% in pAKT and pS6 (compared with baseline), were demonstrated in these patients' paired tumor biopsies (see Figure 4).

**Figure 4 Decrease in PI3K Pathway Activation in Tumor Biopsies Observed upon GDC-0032 Treatment in Both *PIK3CA* MT and WT Tumors**




MT = mutant; NSCLC = non – small-cell lung cancer; WT = wild type.

As of 5 July 2013, metabolic partial responses via FDG-PET (≥20% decrease in maximum standardized uptake value) were observed in 23 out of 38 patients assessed (61%) and included patients from the lowest dose tested (3 mg). Thirteen of these 23 were breast-cancer patients. Of the 13 response-evaluable patients treated with

GDC-0032 plus letrozole, 10 patients (77%) had a partial metabolic response. Of the 15 response-evaluable patients treated with GDC-0032 plus fulvestrant, 11 (73%) had a partial metabolic response.

For additional details, refer to the GDC-0032 Investigator's Brochure.

## 1.8 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Cancer is one of the leading causes of death worldwide, with solid tumors accounting for the majority of these deaths. An estimated 1.38 million women across the world were diagnosed with breast cancer in 2008, accounting for 23% of all cancers diagnosed in women. Breast cancer is the most common cause of death from cancer in women worldwide, estimated to be responsible for almost 460,000 deaths in 2008 (Ferlay et al. 2010).

A neoadjuvant study in a similar patient population with the combination of letrozole and the mTOR inhibitor everolimus has already been completed (Baselga et al. 2009). Please refer to Sections 1.4, 1.5, and 3.3 for further rationale supporting the proposed trial design of combining GDC-0032 with letrozole in the neoadjuvant setting for this patient population. In postmenopausal women with hormone receptor-positive metastatic breast cancer, it is hypothesized that the combination of decreasing estrogen levels with letrozole and inhibition of the PI3K pathway with GDC-0032 may have improved anti-tumor activity as compared to endocrine therapy alone. This is supported by the nonclinical and clinical data outlined below.

GDC-0032 is a potent, selective small molecule inhibitor of Class 1 PI3K that is being developed by Roche/Genentech as an anti-cancer therapeutic agent. Activating and transforming mutations in the p110 alpha subunit of PI3K are commonly found in tumors. GDC-0032 has been shown to be a potent inhibitor of growth in various human cancer cell lines, and especially in nonclinical models of *PIK3CA* MT tumors. In addition, combination activity was demonstrated in the *PIK3CA* WT cell line ZR75-1 when GDC-0032 was added to either fulvestrant or tamoxifen endocrine therapies (combination with letrozole not available in this cell line).

GDC-0032 has also shown additive efficacy in combination with endocrine therapy in a hormone receptor-positive breast cancer xenograft model as outlined in Section 1.6. Nonclinical data support the investigation of GDC-0032 as a single-agent in solid tumors and in combination with endocrine therapy in patients with hormone receptor-positive breast cancer.

Available clinical data with single-agent GDC-0032 suggest that GDC-0032 has dose-linear pharmacokinetics with a half-life of approximately 37−44 hours. Pharmacodynamic markers of PI3K pathway inhibition upon treatment with GDC-0032 have been observed. These include decreases in phospho-S6 in platelet-rich plasma and decreases in F- flurodeoxyglucose-positron emission tomography uptake. Available

clinical data also include multiple confirmed partial responses in patients treated with GDC-0032. These include a patient with *PIK3CA* MT lung adenocarcinoma treated at the 3 mg daily dose and another patient with *PIK3CA* MT, hormone receptor-positive, HER2-positive metastatic breast cancer treated at the 5 mg daily dose. In addition, a patient with *PIK3CA* WT lung cancer treated at the 3 mg daily dose has had prolonged stable disease and remained on study for over 11 months. These data show that single-agent GDC-0032 doses below 6 mg have been shown to have anti-tumor activity. These aggregate data support the use of 6 mg in combination with letrozole.

Letrozole is a marketed product that is approved in the European Union (E.U.) and the United States (U.S.) for the treatment of hormone receptor-positive breast cancer. Based upon the different mechanisms of action of GDC-0032 and the well-established safety profile of letrozole, there are no expected overlapping, significant toxicities between letrozole and GDC-0032.

As of 5 July 2013, efficacy data are available for 24 patients treated with GDC-0032 $capsules$ in combination with letrozole; 3 patients (12.5%) had a partial response as best overall response, 2 of which were confirmed partial responses (cPRs) (1 cPR at 6 mg; 1 cPR at 9 mg). Of the 25 efficacy-evaluable patients treated with GDC-0032 in combination with fulvestrant, 7 patients (28%) had a partial response as best overall response, of which 3 were cPRs (1 cPR at 6 mg; 1 partial response at 9 mg). cPRs have been observed in both *PIK3CA* mutant and *PIK3CA* WT breast cancer patients. Maintenance of cPR has been observed in a patient who had a dose reduction from 6 mg to 3 mg for an adverse event. In addition, no additional safety concerns have been observed with GDC-0032 in combination with letrozole in the ongoing Phase I study compared to GDC-0032 given as single agent.

A number of clinically appropriate strategies to minimize risk to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, protocol design, and management guidelines. These will also be clearly highlighted and discussed in detail at investigator meetings and site visits. In addition, please refer to the GDC-0032 Investigator's Brochure for details regarding potential risks, associated precautions, and other relevant nonclinical and clinical safety information.

Due to the need to develop improved therapies to reverse or delay resistance to current endocrine therapy in HER2-negative, hormone receptor-positive breast cancer and on the basis of the clinical and nonclinical data available for GDC-0032, Genentech/Roche feels that the risk-benefit profile of GDC-0032 in combination with letrozole in postmenopausal patients with HER2-negative, hormone receptor-positive early stage breast cancer is favorable for proceeding with the proposed randomized Phase II clinical trial.

# 2. OBJECTIVES

## 2.1 EFFICACY OBJECTIVES

The primary objective of this study is to evaluate the efficacy of letrozole plus GDC-0032 versus letrozole plus placebo in women with ER+/HER2- early stage breast cancer, as measured by the following co-primary endpoints:

- Tumor overall objective response rate (ORR) by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in all enrolled patients and *PIK3CA* MT patients
- pCR rate in breast and axilla (ypT0/Tis ypN0) by local evaluation in all enrolled patients and *PIK3CA* MT patients

The secondary efficacy objectives of this study are the following:

- Tumor ORR, assessed by centrally assessed breast MRI via modified Response Evaluation Criteria in Solid Tumors (RECIST) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR ypT0/Tis ypN0) by local evaluation in *PIK3CA* WT patients

The following secondary objectives will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of locally assessed ORR *as measured by modified RECIST criteria (Appendix 3)* using the following methods:
    - Breast ultrasound
    - Clinical breast exam (i.e., palpation)
    - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally *derived*, preoperative endocrine prognostic index (PEPI) score upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo.
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment.
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

## 2.2 SAFETY OBJECTIVES

The safety objective for this study is as follows:

- Evaluate the safety of letrozole plus GDC-0032 versus letrozole plus placebo

## 2.3 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for this study are as follows:

- Evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23)

## 2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess whether biomarkers from tumor tissue or blood, including but not limited to somatic cancer associated mutations, PTEN expression, pro-survival pathways (such as PI3K/AKT, MAPK etc.), apoptotic markers, hormone receptor expression levels, and levels of RNA and DNA expression are predictive of response
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to anti-tumor activity
- To assess concordance and percentage of *PIK3CA* mutation status from baseline biopsy and surgical specimen
- To assess emergence of resistance alleles from tumor tissue or blood
- To assess concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response
- To assess the pharmacokinetics and possible drug interaction between letrozole and GDC-0032 upon concomitant administration
- To assess the correlation of GDC-0032 drug levels and GDC-0032 related response (efficacy or adverse events [e.g., colitis, rash])
- To assess the influence of pharmacogenetic polymorphisms on GDC-0032 and/or letrozole on pharmacokinetics and response (either efficacy and/or adverse events)
- Compare the rates of breast-conserving surgery (BCS) and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo.

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF STUDY

This is a two-arm, randomized, double-blind, multicenter, pre-operative study to evaluate the effect of combining letrozole and GDC-0032 versus letrozole and placebo in postmenopausal women with ER+/HER2- untreated, Stage I-III operable breast cancer whose primary tumors are $\geq$ 2 cm. Patients with cT4 or cN3 tumors are not eligible.

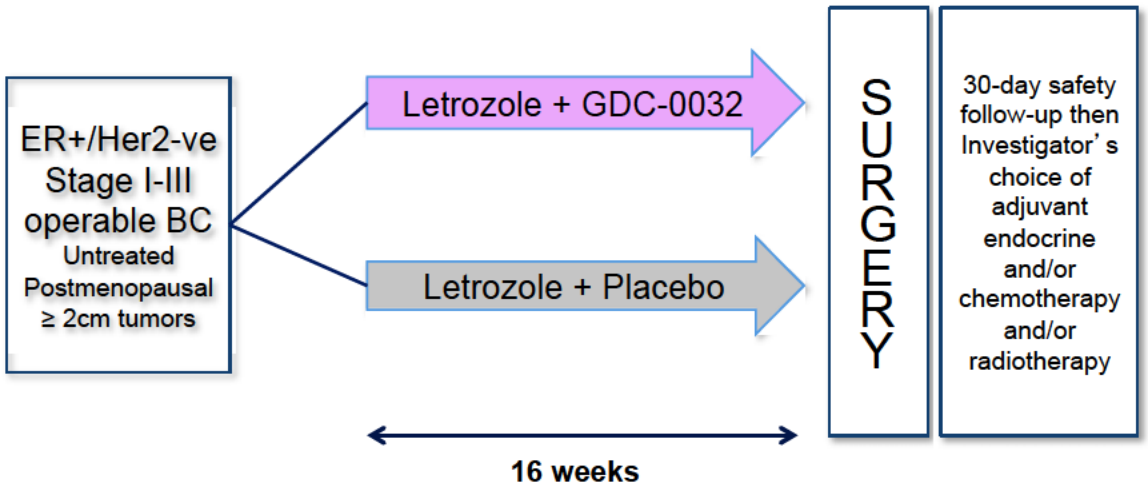
Standard of care assessments/procedures (e.g., bilateral mammogram) performed within 28 days of Day 1 dosing do not need to be repeated for screening purposes.

All patients will undergo pretreatment tumor tissue acquisition (snap-frozen [optimal cutting temperature; OCT] and formalin-fixed paraffin-embedded cores [FFPE]). Two pretreatment FFPE core biopsies and one freshly frozen core biopsy must be obtained for all patients prior to beginning study drug treatment. Tumor tissue from prior diagnostic FFPE core biopsies may be used for enrollment eligibility purposes. For the purpose of enrollment, ER, progesterone receptor (PR), and HER2 will be locally determined prior to beginning of study treatment. Remaining tissue will be retained for future translational studies. Pre-surgical sentinel lymph node biopsy (SLNB) is not allowed.

Patients will be randomized into one of the two treatment arms with a 1:1 randomization ratio. Letrozole at 2.5 mg will be dosed once daily plus either GDC-0032 at $4$ mg $(two\ 2\text{-}mg\ tablets)$ or placebo on a 5 – days-on/ 2 – days-off schedule for a total of 16 weeks (see Figure 5). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

**Figure 5 Study Schema**

Letrozole 2.5 mg QD + GDC-0032 4 mg or placebo QD on a 5 – days-on/2 – days-off schedule




| | Pretreatment | Day 15 (Week 3) | Week 9 | Week 16 | Surgery (Week 17-18) |
|---|---|---|---|---|---|
| Tumor tissue | ● | ● | | | ● |
| MRI | ● | | ● | ● | |
| Breast U/S | ● | | ● | ● | |
| Mammogram | ● | | | ● | |

BC = breast cancer; ER + = estrogen receptor positive; MRI = magnetic resonance imaging; QD = once daily; U/S = ultrasound.

After confirmation of all the eligibility criteria, patients will be randomized to one of the treatment arms. A second biopsy will be performed on Day 15 (Week 3) for biomarker analyses. Biopsies should be performed at least 2 hours after GDC-0032 dose administration.

Randomization will be stratified according to 2 factors:

1. Tumor size (T1-T2 vs. T3)
2. Nodal status (cytologically positive vs. radiologically or cytologically negative)

The study will enroll approximately 330 patients at approximately 110 global sites.

At Weeks 1, 5, 9, 13, and 16 the primary breast tumor and axillary lymph nodes will be assessed by clinical breast examination (palpation and caliper measurement). Suspicion of progression based on clinical exam at any time should be further evaluated (Figure 6).

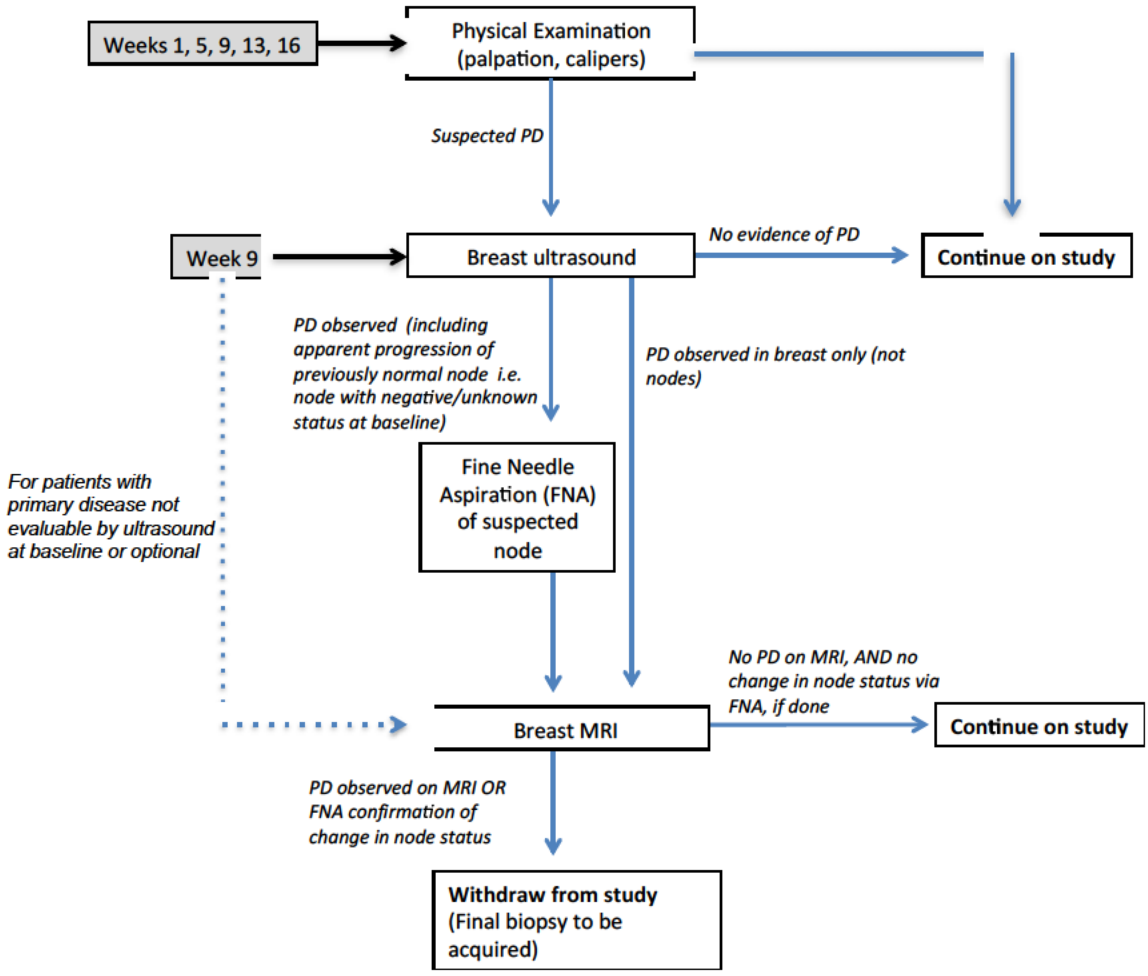
At Week 9, a breast ultrasound will be performed to ensure that there is no progressive disease and for the purpose of surgery planning. Suspicion of progressive disease on breast ultrasound should be confirmed by investigator-assessed breast MRI. Patients with primary disease not evaluable by ultrasound at baseline should be assessed by MRI at Week 9. Suspected progression in nodes should also be confirmed by fine needle aspiration (FNA) if these nodes had not been previously shown to be cytologically positive for cancer. Patients with progressive disease (as defined by modified RECIST, Appendix 3), can either proceed directly to surgery or be taken off of the study, according to the investigator's decision. If the patient goes off-study, every reasonable effort should be made to obtain a new biopsy prior to beginning another systemic treatment.

From Week 13, the patient will visit with the surgeon. The purpose of this visit is two-fold: tentative planning of the type of breast surgery to be performed (breast conservative vs. mastectomy) and scheduling the date for definitive surgery.

During Week 16, breast MRI will be done for the purpose of primary endpoint analysis. Clinical breast exam, breast ultrasound, and mammography will also be conducted prior to surgery for the purpose of the secondary endpoint analysis.

Blood sample for exploratory endpoint analysis will be collected *on Day 1 prior to dosing,* at Week *9*, and prior to surgery.

**Figure 6 Schematic Representing Confirmation of Progression**




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

### 3.1.1 Surgery

Surgery will take place after at least 16 weeks of treatment, during Weeks 17 – 18. Surgery should be performed within 4 days after the last dose of GDC-0032, if possible, to best observe pharmacodynamic knockdown with GDC-0032 in the surgical specimen. Surgery may be delayed due to toxicity or other safety issues, upon discussion with the Medical Monitor (see Section 5.4.1) or recommendations from the Independent Data Monitoring Committee (IDMC; see below). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

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. Surgery specimens will be collected for histological examination to assess for pCR and for other endpoint analyses.

Following surgery, follow-up will proceed according to local standards of care. Adjuvant endocrine therapy and/or chemotherapy will be delivered as per the investigator's choice. Postoperative radiotherapy is required if BCS is performed. In the event of mastectomy, radiotherapy is to be administered according to local guidelines.

A postsurgery visit will be performed 4 weeks (+ 1 week) after surgery, and will mark the end of the study. Assessment of adverse events and general safety will be collected at this visit and the plan for future treatment will be recorded.

The patient should be evaluated at baseline and after Week 13 of treatment for planning the surgical procedure (BCS or mastectomy), and both *the planned and actual surgical treatment* should be documented in the electronic Case Report Form (eCRF).

The co-primary efficacy endpoint, pCR (pCR–ypT0/is, ypN0) will be established via a local review following completion of neoadjuvant therapy and surgery.

Please refer to the pathology manual for further guidance of evaluation for pCR and directions for sending a copy of the pathology report.

A schedule of assessments is provided in Appendix 1.

An Independent Review Facility (IRF) will be used to determine the tumor ORR via MRI. IRF procedures are detailed in the IRF charter.

### 3.1.2 Independent Data Monitoring Committee

An IDMC will monitor accumulating patient safety data at a minimum of once every 6 months until the last patient has completed study treatment. Additional details (e.g., IDMC members, communication, affiliations) will be provided in the IDMC charter.

The IDMC will *review the unblinded* safety *data* after the first 20 patients have *either 1) finished the* 30-day follow-up *visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery), whichever occurs first*. While this review is being conducted, patient accrual into the study will continue. The Medical Monitor may also request additional safety analysis and may call for additional meetings of the IDMC to review ongoing safety data.

## 3.2 END OF STUDY

The end of the study is defined as the date when the last patient has her postsurgery visit. The total duration of the study is expected to be approximately 24 months for enrollment, plus 5.5 months after last patient in.

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Conducting the Study in the Neoadjuvant Setting

Breast cancer is a heterogeneous disease, and not every breast tumor responds equally to a specific agent. Studies based on global gene expression analyses have provided additional insights into this complex scenario. Over the past 10 years, four major classes of breast cancer (Luminal A, Luminal B, HER2-enriched, and basal-like) have been identified and intensively studied (Perou et al. 2000; Sørlie et al. 2001). Known as the intrinsic subtypes of breast cancer, these groups of tumors have revealed critical differences in incidence, survival, and response to treatment. As genomic studies evolve, further sub-classifications of breast tumors are expected to emerge. Thus, a major challenge in breast cancer management is how to prospectively select patients who will derive the maximum benefit from a given drug regimen, minimizing unnecessary toxicities for patients with non-responsive disease.

Neoadjuvant therapy, a systemic therapy administered prior to breast cancer surgery, is now widely used in the 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, especially those with larger tumors. The tumor may shrink prior to surgery, thus increasing the rate of BCS (Coudert et al. 2006), and since the response to therapy can be monitored, the patient might be also spared further treatment with inactive medications.

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 treatment response at a biological level. Finally, the surgical specimen, if pCR is not reached, can be utilized as well. 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 (von Minckwitz and Fontanella 2013; Cortazar et al. 2012).

### 3.3.2 Rationale for Patient Population

Postmenopausal patients with HER2-negative, ER+, early stage breast cancer will be enrolled in this study. This patient population is usually treated with a combination of surgery, anti-hormonal therapy and/or chemotherapy, according to staging and biological features.

Recently, everolimus was approved by the FDA and European Medicines Agency in combination with exemestane for the treatment of advanced or metastatic breast cancer in patients after recurrence or progression following treatment with nonsteroidal AIs. In

the neoadjuvant setting, a combination of letrozole and everolimus resulted in improved responses over letrozole alone in patients with ER+ breast cancer (Baselga et al. 2009).

Important findings in trials with drugs targeting mTOR, like everolimus, *confirm* a *previously identified* pharmacodynamic paradox: while inhibiting mTOR, they lead to an upregulation of the pAKT, resulting in feedback PI3K/AKT/mTOR pathway activation *through an insulin-like growth factor-1 receptor (IGF-1R) mediated feedback loop* (Tabernero et al. 2009). This finding suggests that alternative pharmacologic strategies to shut down the pathway upstream of AKT should be pursued. One of these strategies is to inhibit the PI3K/AKT/mTOR pathway at the PI3K level. PI3K-inhibitors are central regulators of the mTOR signaling pathway, and nonclinical findings show that PI3K-inhibitors and dual PI3K-mTOR inhibitors induce a greater amount of apoptosis than everolimus in estrogen-deprived in vitro models (Sanchez et al. 2011); therefore, it is hypothesized that PI3K-inhibitors may be active and demonstrate greater anti-tumor activity as compared to AIs alone in the neoadjuvant setting.

### 3.3.3 Rationale for Control Group

Aromatase inhibitors (AIs) have been found to be more effective than tamoxifen as a neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer.

Several trials have assessed the efficacy and safety of neoadjuvant endocrine therapy using AIs in patients with postmenopausal breast cancer (Eiermann et al. 2001; Smith et al. 2005; Ellis et al. 2011).

The P024 trial was a worldwide, prospective, randomized, multicenter trial that randomized 337 postmenopausal patients with ER+ breast cancer to receive either 4 months of neoadjuvant letrozole or tamoxifen (Eiermann et al. 2001). The primary endpoint of P024 was the percentage of patients in each treatment arm with objective response as determined by clinical palpation. Secondary endpoints included ORR determined by mammogram and ultrasound, and included the percentage of patients in each arm who had become eligible for BCS. The trial demonstrated a significantly higher clinical response rate for letrozole when compared to tamoxifen (55% vs. 36%; $p < 0.001$) in the intent-to-treat (ITT) population. An improved ORR for letrozole was also observed with ultrasound (35% vs. 25%; $p < 0.042$) and mammogram (34% vs. 16%; $p < 0.001$). The higher response rate assessed by clinical palpation translated into a significantly higher rate of women undergoing BCS in tumors that had initially been considered unsuitable for this procedure (45% vs. 35%; $p = 0.022$). Median time-to-response was 66 days in the letrozole group and 70 days in the tamoxifen group, and both treatments were well tolerated.

The IMPACT trial was a randomized, Phase II, double-blind, double-dummy, multicenter trial that randomly assigned 330 postmenopausal women with ER+ operable or locally advanced, potentially operable breast cancer in a 1:1:1 ratio to receive a daily dose of anastrozole 1 mg and tamoxifen placebo, tamoxifen 20 mg and anastrozole placebo, or

a combination of tamoxifen 20 mg and anastrozole 1 mg for 12 weeks before surgery. The tumor ORR was assessed by both caliper and ultrasound. No significant differences in ORR in the ITT population between patients receiving tamoxifen, anastrozole, or the combination were seen. However, in a predefined analysis, there was a nonsignificant trend towards more patients requiring mastectomy at baseline actually receiving BCS with anastrozole than with tamoxifen (44% vs. 31%, respectively; $p = 0.23$); this difference became significant for patients deemed by their surgeon to be eligible for BCS after treatment (46% vs. 22%, respectively; $p = 0.03$). All treatments were well tolerated.

The ACOSOG Z1031 trial compared three AIs in a randomized, Phase II, neoadjuvant trial designed to select agents for Phase III investigations. Three hundred seventy-seven postmenopausal women with clinical Stage II to III ER+ breast cancer were randomly assigned to receive neoadjuvant exemestane, letrozole, or anastrozole. The primary endpoint was clinical response. No formal comparison between arms was pre-specified in the statistical plan. ORR was 62.9%, 74.8%, and 69.1% for the exemestane, letrozole and anastrozole arms, respectively. On the basis of clinical response rates, letrozole and anastrozole were selected for further investigation; however, no other differences in surgical outcome, PEPI score, or Ki67 suppression were detected. The BCS rate for mastectomy-only patients at presentation was 51%.

Results from these trials suggest that neoadjuvant endocrine therapy can be beneficial in postmenopausal patients with hormone-sensitive breast cancer, and that it offers an alternative to neoadjuvant chemotherapy.

### 3.3.4 Rationale for the Efficacy Outcome Measure of Response Rate Assessed by Magnetic Resonance Imaging

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, non-registrational, neoadjuvant trials in combination with endocrine therapy (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 computed tomography (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 (Akazawa et al. 2006; Balu-Maestro et al. 2002; Yeh et al. 2005), including the I-SPY trial (Hylton et al. 2012). For these reasons, ORR as assessed by breast MRI has been chosen as a co-primary endpoint for this trial.

#### 3.3.4.1 Rationale for Efficacy Outcome Measure of Pathologic Complete Response

pCR is a recognized efficacy endpoint of neoadjuvant trials, especially those with neoadjuvant chemotherapy, as it has been correlated with long-term outcomes, such as event-free survival (von Minckwitz and Fontanella 2013).

In trials of neoadjuvant hormonal therapy, pCR is an unlikely event. For instance, in the neoadjuvant trial comparing everolimus plus letrozole to letrozole, pCR rates were 1.4% and 0.8%, respectively (Baselga et al. 2009).

In the ongoing Phase I/II trial that combines letrozole with GDC-0032, tumor shrinkage has been observed, and some patients presented sustained partial responses. As pCR is a recognized indicator of activity to a given regimen, it would be useful to assess it as a co-primary efficacy endpoint of this trial. Furthermore, for the same trial size, this would represent a minimal increase in the minimum detected difference (MDD) of the co-primary endpoint for pCR ORR (from MDD of 12% to MDD of 13%).

In September of 2013, the FDA granted accelerated approval of Perjeta as part of a complete treatment regimen for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer in the neoadjuvant setting.

#### 3.3.4.2 Rationale for Ki67 Measurements

Ki67 is a well-established proliferation biomarker with prognostic value in ER+ breast cancer (Dowsett et al. 2011). Efficacy of endocrine therapy relies on induction of cell-cycle arrest, and during neoadjuvant treatment, Ki67 levels reflect the ability of endocrine agents to suppress proliferation (Smith et al. 2005; Ellis et al. 2011). In the neoadjuvant trial of letrozole with everolimus, by using the definition that patients with natural log (Ki67) $< 1$ at Day 15 have an antiproliferative response, 57% of everolimus-treated patients were responders vs. 30% in the placebo arm, with a significant p value of $< 0.01$ (Baselga et al. 2009). Furthermore, the mean reduction in the percentage of Ki67-positive tumor cells at Day 15 relative to baseline was greater in the everolimus-treated patients ($90.7\% \pm 3.2\%$) than in the placebo group ($74.8\% \pm 6.8\%$; $p = 0.0002$). In the IMPACT trial, Ki67 was assessed at baseline, on Day 15, and at surgery (Smith et al. 2005). For each treatment arm, the reduction in geometric mean Ki67 levels was significantly higher for anastrozole than for tamoxifen at both time points ($p = 0.004$, $p = 0.001$, respectively), but no differences were found between tamoxifen and the combination. In the ASCOSOG Z1031 trial (Ellis et al. 2011), although no data on Ki67 at Day 15 were available, no differences were found between treatments at baseline and at surgery (after $16 - 18$ weeks of therapy). The geometric mean percentage change in Ki67 for each treatment was similar between the arms (anastrozole 78%, exemestane 81.2%, and letrozole 87.1%).

The issue of whether Ki67 decrease at surgery or at any timepoint during treatment correlates with long-term efficacy outcomes has been addressed in the P024 trial

(Eiermann et al. 2001). Treatment with letrozole led to higher, treatment-induced reduction of Ki67 levels in the tumor at surgery (87% reduction in the letrozole arm vs. 75% in the tamoxifen arm; analysis of covariance $p = 0.0009$) based on the 185 specimens with available data on Ki67 (Ellis et al. 2003). With a median follow-up of 61.2 months, low levels of Ki67 in the biopsy at the end of treatment were significantly associated with better relapse-free survival (RFS; HR 1.4 per natural log increase in the Ki67 value, 95% CI 1.2 – 1.6, $p < 0.001$), and breast cancer specific survival (HR 1.4, 95% CI 1.1 – 1.7, $p = 0.009$). Finally, in the IMPACT trial, higher Ki67 expression after 2 weeks of endocrine therapy was statistically significantly associated with lower RFS ($p = 0.004$), whereas higher Ki67 expression at baseline was not (Smith et al. 2005).

Importantly, the Ki67 suppression in these hormonal neoadjuvant trials mirrored efficacy outcomes in large adjuvant trials: adjuvant BIG1-98 trial ($n = 8,010$) showed the superior efficacy of letrozole over tamoxifen (Regan et al. 2011), similar to the neoadjuvant P024 trial ($n = 185$); the adjuvant ATAC trial ($n = 9,366$) showed that anastrozole was better than tamoxifen and the combination of anastrozole plus tamoxifen (Cuzick et al. 2010), similar to neoadjuvant IMPACT ($n = 259$); and the adjuvant MA27 trial ($n = 7,576$) showed similar efficacy of anastrozole and exemestane (Goss et al. 2013), mirroring neoadjuvant ACOSOG Z1031 ($n = 266$). These results suggest that a biological superiority hypothesis generated by a neoadjuvant study may help the design of future adjuvant hormonal therapy trials.

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

#### 3.3.4.3 Rationale for Using the Preoperative Endocrine Prognostic Index Score

In addition to Ki67, pathologic tumor size (T1 or T2 versus T3 or T4), node status (positive or negative), and the ER status (positive Allred score 3–8 versus negative Allred score 0–2) of the surgery specimen were also determined to have independent prognostic value for relapse and death after relapse in the P024 trial (Ellis et al. 2008). A PEPI score, prognostic for RFS, which weighs each of these factors according to their associated hazard ratios, was developed and subsequently validated in an independent data set from the IMPACT trial (Ellis et al. 2008). No relapses were recorded in either trial in patients with tumors classified as T1N0 and with a PEPI score of 0 (residual tumor with a Ki67 level $\leq 2.7\%$, and with maintained ER expression) or in the rare patient with a pCR.

In this trial, the PEPI score will be *derived* centrally.

#### 3.3.4.4 Rationale for Assessing ORR by Clinical Breast Exam (Palpation), Mammography, and Breast Ultrasound

Objective overall response rate will also be assessed by clinical breast exam, mammography, and breast ultrasound during screening and prior to surgery. These data will allow for more direct comparison of results to other neoadjuvant trials with endocrine therapy as described in Section 3.3.3. The concurrent acquisition of ORR data with these techniques, in addition to MRI-based measures, will also provide valuable comparative information on these methods, which will be important for both future neoadjuvant studies and GDC-0032 clinical development.

#### 3.3.4.5 Rationale for Assessing Enhancing Tumor Volume by Breast Magnetic Resonance Imaging

As shown in the I-SPY trial, tumor volume measurements based on the percent of tumor with enhancing signal after contrast agent administration may be a more sensitive measure of response during neoadjuvant treatment than longest dimension measures (Hylton et al. 2012). However, there are no established response criteria for volumetric data, and the extrapolation of current one- and two-dimensional criteria to volumetric data based on a spherical model may not be appropriate given the range of tumor morphologies expected in this population of patients (Loo et al. 2011). Additionally, there are only very limited data on the clinical relevance of any particular range in change in tumor volume during the course of neoadjuvant treatment. For these reasons, changes in enhancing tumor volume as measured by breast MRI will be a secondary endpoint in the trial.

### 3.3.5 Rationale for Independent Review Facility

Due to the relatively novel nature of using MRI as an imaging endpoint, a central assessment by an IRF for the co-primary endpoint of response rate via MRI will be performed to ensure consistency across all sites participating in the study.

### 3.3.6 Rationale for Interim Safety Review

The first 20 patients will be assessed for safety following surgery and 30 days beyond. This will allow the IDMC to review all safety data during the treatment period and to evaluate any surgery complications that may be attributed to GDC-0032.

### 3.3.7 Rationale for GDC-0032 Dosage

As of 5 July 2013, 34 patients have been enrolled into the dose-escalation stage of Study PMT4979g, and 56 patients have been enrolled into the single-agent expansion cohorts at 9 mg in Stage 2 (Cohorts A-D and G). *All patients received GDC-0032 in capsules.* Five dose-escalation cohorts (i.e., 3, 5, 8, 12, and 16 mg daily) were tested *(see Section 1.7.1).* The maximal administered dose was 16 mg. To obtain more safety data on long-term tolerability, the recommended single-agent dose and schedule for the single-agent GDC-0032 expansion stage is 9 mg daily.

Of the 19 efficacy-evaluable patients treated with GDC-0032 in combination with letrozole, one patient at 6 mg had a cPR. The *PIK3CA* mutation status of this patient is unknown. Since efficacy has been observed at 6 mg, and the long-term safety suggests that 6 mg is better tolerated, the neoadjuvant study will utilize 6 mg GDC-0032 in combination with letrozole.

Of the 27 efficacy-evaluable patients treated with GDC-0032 in combination with fulvestrant, 2 confirmed partial responses were observed at 6 mg and 1 confirmed partial response at 9 mg.

Colitis has been observed with an incidence rate of 6.2% (10/160 patients). The time (from the first dose of study treatment) to onset of colitis ranged from approximately 82 – 248 days as either a single agent or in combination with letrozole or fulvestrant. Most of the colitis cases have been observed at the 9-mg dose level or higher. Most of the colitis cases have been observed at the 9-mg dose level or higher. To mitigate the late-onset adverse events, such as colitis, an intermittent dosing schedule will be applied. With the 40-hour half-life, a limited impact on efficacy is anticipated. PK modeling has shown that a schedule of 5 days on/2 days off will maintain GDC-0032 drug exposure levels within an efficacious range as assessed by various breast cancer cell lines. There has also been data presented for another PI3K inhibitor BKM120 with a similar half-life in combination with letrozole in a Phase Ib study that demonstrated improved tolerability with similar efficacy for a schedule of 5 days on/2 days off as compared to daily continuous dosing of the PI3K inhibitor (Mayer et al. 2012).

### 3.3.8 Rationale for Biomarker Assessments

Breast cancer is a heterogeneous disease, and *PIK3CA* mutations have been shown to vary among patients (CGAN 2012). Therefore, all patients may not equally likely benefit from treatment with GDC-0032. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with *PIK3CA*-driven pathogenesis who are most likely to respond to GDC-0032. Pharmacodynamic biomarkers will be *evaluated* to assess the biologic activity of the addition of GDC-0032 to letrozole.

It has been suggested that not all molecular alterations in the PI3K/AKT/mTOR pathway result in pathway activation. In a comprehensive analysis of tumors from 850 breast cancer patients, protein markers of PI3K/AKT/mTOR pathway activation (pAKT, pS6, and p4EBP1) correlated strongly with *INPP4B* and PTEN loss, to a degree with *PIK3CA* amplification, but were not elevated in *PIK3CA*- MT luminal A cancers (CGAN 2012). This apparent disconnect between the presence of *PIK3CA* mutations and biomarkers of pathway activation had been previously noted (Loi et al. 2010), and stress the need to find innovative and robust predictive biomarkers to PI3K/AKT/mTOR pathway inhibiting agents (Saini et al. 2013).

Next generation sequencing (NGS) techniques, like deep genome sequencing, may offer a unique opportunity to identify such biomarkers of response. For example, using whole

genome sequencing, a two base-pair deletion in the *TSC1* gene was found in a metastatic bladder cancer patient with a prolonged response ($>2$ years) to everolimus as single agent (Iyer et al. 2012). Among 13 additional bladder cancer patients treated with everolimus in the same trial, those with *TSC1* mutant tumors remained on therapy longer than those with WT tumors (7.7 vs. 2.0 months, $p=0.004$), suggesting that mTORC-1 directed therapies may be most effective in cancer patients whose tumors harbor *TSC1* somatic mutations. Similar approaches could be of great value when analyzing responses to agents targeting the PI3K/AKT/mTOR pathway, especially in the neoadjuvant setting.

In addition to mutational activation of proteins, levels of RNA and DNA can also activate the PI3K pathway. For example, increases in DNA copy number in receptor tyrosine kinases such as FGFR1/2 and IGF-1R, which occur at some frequency in breast cancer, can activate downstream PI3K pathway. Hormone receptor positive breast cancer can be divided into luminal A and luminal B subtype, with the luminal B subtype displaying a higher proliferative index. Therefore, profiling the RNA and DNA expression of tumors will allow intrinsic subtyping of patients enrolled onto study. In addition, PI3K transcription activation signatures may identify additional patients who could respond to PI3K inhibitors outside of *PIK3CA* mutations.

The use of circulating tumor DNA (ctDNA) to monitor response to treatment is an area of great interest. It could allow for an early, non-invasive, and quantifiable method for use in the clinical setting to identify candidates for specific therapies and monitoring of disease mutation status over time (Higgins et al. 2012). The neoadjuvant setting is ideal to prospectively test these approaches.

### 3.3.9 Rationale for Day 15 Biopsy

On-study biopsies can provide valuable information regarding target engagement and downstream pathway suppression. Assessing how GDC-0032 interacts with letrozole in this previously untreated patient population provides a unique opportunity to understand the interaction between two anti-cancer molecules. When available, FFPE tumor samples will be assessed for pathway modulation using immunohistochemistry (IHC) methodologies, and fresh frozen OCT samples will be assessed using reverse phase protein array (RPPA) technologies, or equivalent. Measurement of Ki67 after 2 weeks of continuous letrozole and GDC-0032 combination treatment versus letrozole and placebo will give a good benchmark to prior neoadjuvant studies that demonstrated a larger decrease in Ki67 at this 2-week timepoint for a combination of letrozole and everolimus as compared to letrozole and placebo (Baselga et al. 2009). This Day 15 biopsy will also be useful in identifying potential biomarkers that may help predict a tumor response for patients treated with GDC-0032.

### 3.3.10 Rationale for Collection of Blood Sample for the Detection of Plasma Protein Biomarkers

Emerging evidence indicates that increases in levels of systemic cytokines and chemokines, such as receptor tyrosine kinase growth factors, can attenuate response to drugs, particularly targeted agents such as GDC-0032 (Wilson et al. 2012). Assays to assess the expression of soluble, systemic cytokines and chemokines from the plasma of patients will be carried out using ELISA-based mass spectrometry or equivalent methodologies.

### 3.3.11 Rationale for Collection of Blood Sample for DNA Sequencing to Identify Mutations in Plasma

There is increasing evidence that circulating DNA obtained from blood specimens of cancer patients is representative of the DNA and mutational status of tumor cells (Diehl et al. 2008; Maheswaran et al. 2008). Assays are available that can detect the major PI3K mutations (and other cancer-related genes) in plasma, and results from this analysis will be correlated with tumor specimens.

### 3.3.12 Rationale for Collection of Blood Sample for Next Generation Sequencing

Next generation sequencing (NGS) technologies generate a large quantity of sequencing data. Tumor DNA can contain both reported and unreported chromosomal alterations due to tumorigenesis process. To help control for sequencing calls in previously unreported genomic alterations, a normal blood sample will be taken during pre-screening to determine whether the alteration is somatic or germline.

### 3.3.13 Rationale for Pharmacokinetic Sample Collection Schedule

PK samples will be collected from early breast cancer patients in this study to assess the pharmacokinetics of GDC-0032 and possible DDI between letrozole and GDC-0032 in this population. Considering the lack of DDI between GDC-0032 and letrozole upon concomitant administration in the 24 metastatic breast cancer patients in the Phase I study (preliminary data), this drug interaction in early breast cancer patients is unlikely. Hence, extensive PK sample collection is not needed; sparse PK sampling from patients enrolled in this study is adequate. The proposed PK sample collection schedule will also enable assessment of a concentration and response relationship to better understand the following: pharmacokinetics/pharmacodynamics (efficacy), PK/safety correlation, and population pharmacokinetics. Additional PK samples may be collected for safety concerns (e.g., severe adverse event) in order to better characterize drug levels in these patients at the time of the adverse event.

### 3.3.14 Rationale for the Collection of DNA for Exploratory Pharmacogenetic Polymorphisms

One sample (approximately 3 mL of whole blood) will be collected from all patients using K3-EDTA collection tubes. Samples will be used for the evaluation of genetic

polymorphisms of drug metabolic enzymes including, but not limited to, CYP2C9, CYP3A4/5, and UGT1A1, and transporters (e.g., OATP1B1) and for genetic variants which could contribute to potentially drug-related rash and/or colitis safety assessments (including but not limited to human leukocyte antigen [HLA]). For sample handling procedures, storage conditions, and shipment instructions, see the laboratory manual. Only in circumstances where there is concern for collection of this genetic material for above evaluations, can this assessment be considered not mandatory as part of study assessments in this study. Results of any analyses from these samples will be reported outside the clinical study report.

It is established that genetic variants of drug-metabolizing enzymes and transporters can affect the pharmacokinetics of drugs, which affects their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1, which facilitates the metabolism and excretion of SN 38 (the active metabolite of irinotecan), are at higher risk for adverse effects associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006). Preliminary results from in vitro metabolism studies with GDC-0032 suggest that they are partially metabolized by multiple Phase I cytochrome P450 enzymes, including CYP3A4. Although in vitro studies can help elucidate the roles of enzymes in the metabolism of the drug, these results are not always predictive of in vivo metabolism for a number of reasons, such as differences in drug concentrations that the enzymes encounter in vitro and in vivo. For this reason, a blood sample for DNA isolation is proposed to be collected from all patients in this study for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics or response to GDC-0032. The decision to analyze the samples will be based on a review of the pharmacokinetics and response data. Most recently, the role of HLA has been demonstrated to play an important role in the development of drug-induced rash for some drugs (carbamazepine, abacavir, and allopurinol). Therefore, evaluation of genetic variants of genes that may regulate the immune response (including but not limited to HLA) may also be investigated to characterize unusual safety responses that are not predicted by GDC-0032 pharmacokinetics.

The analysis will be performed on identifiable DNA samples, because it is necessary to link a patient's PK data with genotype. This analysis would be restricted to the evaluation of genes that may be involved in the pharmacokinetics of GDC-0032, drug metabolism, disposition, or elimination and/or response of patients who develop severe adverse reactions such as colitis or rash. Samples may be stored and analyzed up to 15 years after the completion of the study, at which time all DNA samples collected for this analysis will be destroyed.

### 3.3.15 Rationale for Patient-Reported Outcome Assessments

A PRO is "any report on the status of a patient's health condition that comes directly from the patient, without any interpretation of the patient's response by a clinician or

anyone else" (FDA Guidance for Industry 2007). PRO measures are able to contextualize a patient's experience on trial, elucidating symptom and treatment burden. Since early breast cancer is often asymptomatic, the PRO objective is to evaluate and compare PROs of treatment-related symptoms, patient functioning, and the health-related quality of life between treatment arms (Lemieux et al. 2011).

The EORTC QLQ-C30 and associated breast cancer module, QLQ-BR23, were selected because they were specifically developed to assess the most salient constructs and experiences with breast cancer and its treatment. The EORTC QLQ-C30 is a widely and frequently used PRO measure in oncology trials that contains a global health status scale, functional scales (physical, role, emotional, cognitive, and social), and general cancer symptom scales/items with a recall period of 'the past week.'

The second measure, the QLQ-BR23, is a breast cancer specific modular supplement to the EORTC QLQ-C30, and includes additional functioning scales and symptom scales/items relating to breast cancer.

These instruments demonstrate strong psychometric properties, of both reliability and validity, and meet the requirements for this study (EORTC QLQ-C30 Scoring Manual, 1999). Therefore, PRO data will be collected from patients using the EORTC QLQ-C30 and modified QLQ-BR23 (Quinten et al. 2009).

## 3.4 OUTCOME MEASURES

### 3.4.1 Efficacy Outcome Measures

#### 3.4.1.1 Co-Primary Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

- Tumor ORR, via centrally assessed breast MRI via modified RECIST (Appendix 3) in all enrolled patients and *PIK3CA* MT patients.
- pCR rate in breast and axilla (total pCR) as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system (Appendix 6) by local evaluation in all enrolled patients and *PIK3CA* MT patients.

#### 3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Tumor ORR, assessed by centrally assessed breast MRI via modified RECIST (Appendix 3) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR) by local evaluation in *PIK3CA* WT patients.

The following secondary outcome measures will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of ORR, as measured by modified RECIST criteria (Appendix 3) using the following methods:
    - Breast ultrasound
    - Clinical breast exam (i.e., palpation)
    - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally *derived* PEPI score upon treatment with letrozole plus GDC-0032 with letrozole plus placebo
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) yoT0/is, ypNX (breast pCR)

### 3.4.2 Safety Outcome Measures

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE, v4.0
- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Serious adverse events
- Protocol-defined adverse events of special interest
- Clinically significant changes in vital signs and in clinical laboratory results during the adverse event reporting period (see Section 5.3.1)

### 3.4.3 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- HRQoL, including side-effects of therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems), and patient functioning as measured using the EORTC QLQ–C30 and the modified breast cancer module QLQ–BR23

### 3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- ORR, pCR rate, and PEPI scores according to the decrease in Ki67 after 2 weeks of letrozole plus GDC-0032 and letrozole plus placebo.
- Expression of biomarkers before, during, and after therapy. These include, but are not limited to, the following:
    - PI3K pathway aberrations
    - Gene signatures, including intrinsic subtyping and PI3K pathway activity
    - Hormone receptor expression levels
    - Protein and phospho-protein markers and combinations
    - Mutations within cancer-associated genes
    - Copy number alterations in cancer-related genes
    - Plasma-based protein biomarkers
    - ctDNA
- Compare the rates of BCS and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo
- The relationship between GDC-0032 concentration and tumor response and/or drug safety response
- Letrozole concentrations with and without administration of GDC-0032
- The relationship between pharmacogenetic differences in drug metabolizing enzymes and transporters and other patient-specific covariates with PK of GDC-0032 or letrozole and/or drug response
- Changes from baseline to surgery in the apparent diffusion coefficient (ADC), a marker of tumor cellularity derived from diffusion-weighted MRI
- Concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response

## 4. MATERIALS AND METHODS

### 4.1 PATIENTS

Patients for this study include postmenopausal patients with ER+/HER2- untreated, Stage I-III operable breast cancer. The size of the primary tumor should be $\geq$2 cm by MRI.

### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF) prior to any study-specific procedure
- Female patients
- Postmenopausal status and age $\geq$18 years. Postmenopausal status is defined as follows:
  - Age $\geq$ 60 years or
  - Age $<$ 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment or
  - Prior bilateral oophorectomy ($\geq$ 28 days prior to Day 1 of treatment)
- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor $\geq$ 2 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 $\geq$ 2 cm and designated as the "target" lesion for all subsequent tumor evaluations.
  - Stage I to operable Stage III breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms).
- ER-positive and HER2-negative breast cancer, as per local laboratory or regional definition
- Breast cancer eligible for primary surgery
- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for *PIK3CA* mutation status by central histopathology laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Fasting glucose $\leq$125 mg/dL
- Adequate hematological, renal, and hepatic function, as follows:
  - Absolute neutrophil count $\geq$ 1500/$\mu$L
  - Platelets count $\geq$100,000/$\mu$L
  - Hemoglobin $\geq$ 9 g/dL
  - Serum bilirubin $\leq$ 1.5$\times$ the upper limit of normal (ULN)
  - Patients with known Gilbert's disease who have serum bilirubin $\leq$ 3 $\times$ ULN may be enrolled
- Aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase $\leq$1.5$\times$ ULN

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation:

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

- International normalized ratio (INR) $< 1.5 \times$ upper limit of normal (ULN) and activated partial thromboplastin time (aPTT) $< 1.5 \times$ ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2–3 is required. If anticoagulation is required for a prosthetic heart valve, then INR should be between 2.5–3.5.

- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Ability and willingness to comply with study visits, treatment, testing, and to comply with the protocol, in the investigator's judgment

### 4.1.2 Exclusion Criteria

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

- Any prior treatment for primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer
- 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 sentinel lymph node biopsy prior to study treatment
- Patients for whom upfront chemotherapy is clinically judged appropriate as optimal neoadjuvant treatment
- Patients for whom immediate surgery is indicated
- Type 1 or 2 diabetes requiring antihyperglycemic medication
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteric absorption
- History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis)
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF)$>$ 470 msec
- DLCO $<$ 60% of the predicted values (see Appendix 7 for calculations)
- Clinically significant (i.e., active) cardiovascular disease, uncontrolled hypertension, unstable angina, history of myocardial infarction, cardiac failure class II-IV (New

York Heart Association, Appendix 5), or any other that in the judgment of the investigator could jeopardize patient safety or study outcomes

- 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
- Active infection requiring intravenous (IV) antibiotics
- Patients requiring any daily supplemental oxygen
- Clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis
- Known human immunodeficiency virus (HIV) infection
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications
- Significant traumatic injury within 3 weeks prior to initiation of study treatment
- Major surgical procedure within 4 weeks prior to initiation of study treatment
- Inability to comply with study and follow-up procedures
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

### 4.2.1 Patient Randomization

After written informed consent has been obtained and eligibility has been established, the study site will obtain a patient's identification number and treatment assignment using a permuted block randomization algorithm via an interactive voice or web-based response system (IxRS).

### 4.2.2 Stratification

Patients will be randomized into one of the two treatment arms in a 1:1 ratio based on the following stratification factors:

- Tumor size (T1-2 vs. T3)
- Nodal status (cytologically positive vs. radiologically or cytologically negative). If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then fine needle aspiration (FNA) or core biopsy is required to confirm nodal status.

### 4.2.3 Blinding

Investigators and patients will be blinded to treatment assignment of GDC-0032 or placebo.

For emergency situations, the investigator will be able to break the treatment code by contacting the IxRS. The responsibility to break the treatment code in emergency situations resides solely with the investigator. For non-emergency situations, the investigator needs to obtain approval from the Medical Monitor to break the treatment code. Unblinding during the study will result in the withdrawal of a patient from the study. For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected, suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. The PK assay group will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed and bioanalytical methodology to employ. However, the PK scientist does not have access to the PK assay results and therefore stays blinded until the PK assay results need to be interpreted and reported. Samples from patients assigned to the comparator arm will be analyzed for letrozole. However, GDC-0032 assay will be analyzed by request (i.e., to evaluate a possible error in dosing).

## 4.3 STUDY TREATMENT

### 4.3.1 Formulation, Packaging, and Handling

#### 4.3.1.1 GDC-0032 and Placebo

GDC-0032 Drug Substance and Drug Product are manufactured according to current Good Manufacturing Practice guidelines for use in the clinical studies. Each lot of GDC-0032 for clinical studies is subjected to a series of quality control tests to confirm its identity, purity, potency, and quality.

GDC-0032 is provided for use in clinical studies as a white, film-coated, immediate-release tablet formulation of *2* mg strength.

Placebo tablets will be identical in shape and color to the 2-mg tablets of GDC-0032 and will be indistinguishable from the 2-mg tablets of GDC-0032. The ingredients in the placebo tablets are identical to those in the 2-mg tablets of GDC-0032, except for the absence of GDC-0032 active.

The GDC-0032 active and placebo tablets are packaged in high-density polyethylene bottles, are labeled for clinical use, and should not be stored above 25°C.

For further details, see the GDC-0032 Investigator's Brochure.

#### 4.3.1.2 Letrozole

Letrozole will be labeled according to regulatory requirements in each country, as well as in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and will be labeled for investigational use only. The Sponsor will provide letrozole free of charge to all study sites.

Refer to the letrozole (e.g., Femara®) Package Insert or summary of product characteristics (SmPC) for details on the formulation and storage of letrozole.

### 4.3.2 Dosage, Administration, and Compliance

#### 4.3.2.1 GDC-0032 and Placebo

Patients will receive an oral, daily dose of 4 mg *(two 2-mg tablets)* GDC-0032 or placebo on a schedule of 5 days on/2 days off for a maximum of 16 weeks. Patients will take GDC-0032 *or placebo* at the same time of day ±2 hours, unless otherwise instructed. Patients will be instructed as to the number of tablets to take. Patients will be asked to record the time and date that they take each dose in a medication diary.

If a patient misses a GDC-0032 or placebo dose or vomits up a tablet, she should be instructed to skip that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up. Patients will be instructed to bring their medication diary to each study visit for assessment of compliance. Patients will also be instructed to bring all unused tablets to each study visit for GDC-0032 or placebo accountability.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

#### 4.3.2.2 Letrozole

Patients will receive an oral, daily dose of 2.5 mg letrozole for 16 weeks (or until time of surgery at the investigator's discretion). No dose modifications of letrozole are permitted. Any overdose or incorrect administration of letrozole should be noted on the letrozole

Administration eCRF. Adverse events associated with an overdose or incorrect administration of letrozole should be recorded on the Adverse Event eCRF.

*Both GDC-0032 or placebo and letrozole should be taken together (in no particular order) at the same time each day ± 2 hours, unless otherwise instructed.*

### 4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (letrozole and GDC-0032) will be provided by the Sponsor where required by local health authority regulations. The investigational site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) 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 GDC-0032

The Sponsor will offer post-trial access to the study drug (GDC-0032, letrozole, or other study interventions) 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 would not 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 untreated, postmenopausal ER+/HER2−, early stage, operable breast cancer

- The Sponsor has reasonable safety concerns regarding the study drug as treatment for untreated, postmenopausal postmenopausal ER+/HER2−, early stage, operable breast cancer
- 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
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 7 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

GDC-0032 was metabolized primarily by CYP3A4 in HLM and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low-to-moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a pharmacokinetic DDI.

Letrozole is mainly metabolized to a pharmacologically inactive carbinol metabolite by CYP2A6 and CYP3A4 in vivo. GDC-0032, which has the potential to induce CYP3A4 based on in vitro induction studies, was administered in combination with letrozole in the expansion phase of Study PMT4979g to assess their DDI potential. Preliminary data from 10 patients in this cohort indicated that steady state plasma concentrations of both letrozole and GDC-0032, following once daily administration of the combination (2.5 mg letrozole plus 6 or 9 mg GDC-0032), were similar to historical, single-agent data suggesting lack of DDI between GDC-0032 and letrozole. These preliminary results suggest that GDC-0032 and letrozole combination may be administered without the risk of a pharmacokinetic DDI.

In vitro CYP inhibition studies in HLMs and induction studies in human hepatocytes suggested a low to moderate potential of GDC-0032 to perpetrate DDIs. A clinical DDI study with rifampin (CYP3A4 inducer) and itraconazole (CYP3A4 inhibitor), to understand the effect of CYP inhibitors or inducers on the pharmacokinetics of GDC-0032, is currently ongoing (Study GP28617).

### 4.4.2 Prohibited Therapy

Prohibited therapy is as follows:

- **Anti-cancer therapy:** No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than letrozole permitted in this protocol) will be allowed.
- **Hormone replacement therapy**, **topical estrogens (including any intra-vaginal preparations), hormonal contraception, megestrol acetate, and selective estrogen-receptor modulators used with prophylactic intent**: If a patient is receiving these at the moment of registration, treatment should be discontinued prior to randomization.
- **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.
- **Potent CYP3A4 inhibitors:** Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole and itraconazole) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If a strong CYP3A4 inhibitor is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.
- **Potent CYP3A4 inducers:** Concomitant use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, phenobarbital) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to induce CYP3A4. If a strong CYP3A4 inducer is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.

## 4.5 STUDY ASSESSMENTS

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

### 4.5.1 Informed Consent Forms and Screening Log

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

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

### 4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases that are currently active or that were active within the previous 5 years, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within *7* days prior to the screening visit.

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

### 4.5.3 Physical Examination

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems as well as weight and height (height is measured at the screening visit 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), limited, symptom-directed physical examination may be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

### 4.5.4 Vital Signs

Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. *Oxygen saturation is obtained by pulse oximetry after the patient has been in a seated position for ≥5 minutes. Obtain vital signs predose.*

### 4.5.5 Electrocardiograms

Triplicate electrocardiogram (ECG) recordings will be obtained at each specified timepoint (see the schedule of assessments in Appendix 1).

### 4.5.6 Distant Sites Tumor Assessment

Baseline distant sites tumor staging procedures should be performed in alignment with National Comprehensive Cancer Network (NCCN) or national guidelines, within 28 days prior to randomization.

As a reference, as per NCCN guidelines, staging procedures are based on clinical stage:

- 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.

- For Stage IIIB and Stage IIIC: bone scan and CT of chest, abdomen, and pelvis should be conducted for all patients.

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.

### 4.5.7 Tumor and Response Evaluations

All measurable disease must be documented at screening and reassessed at subsequent timepoints as outlined in Appendix 1. Responses based on clinical breast exam, breast ultrasound, and mammography will be investigator-assessed. Whenever possible, assessments should be performed by the same evaluator to ensure internal consistency across visits. Response via breast MRI will be centrally assessed, and all assessments will be based on modified RECIST criteria (see Appendix 3).

**Clinical Breast Examination:** Assessment of primary breast tumor and regional lymph nodes must be done by physical examination (palpation) during baseline evaluation, Weeks 1, 5, 9, 13 and 16 during the treatment phase, and prior to surgery. Breast tumor measurement by caliper (preferred) or rule 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.

**Mammogram:** Bilateral mammograms must be obtained at baseline within 28 days prior to enrollment and again prior to surgery. Mammographic tumor measurements are to be recorded in the eCRF.

**Breast Ultrasound:** Bilateral breast ultrasounds must be obtained at baseline within 28 days prior to enrollment. Investigator decision whether to perform unilateral or bilateral ultrasounds performed at Week 9 and prior to surgery (Week 16) may be unilateral or bilateral and per investigator discretion. If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then FNA or core biopsy is required. Sonographic tumor measurements are to be recorded in the eCRF. The tumor site may be marked with a radiopaque clip or marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy.

**Breast MRI:** Contrast-enhanced breast MRI scans will be mandatory for all study patients at baseline (within 28 days prior to enrollment) and prior to surgery (Week 16). MRI is optional at Week 9, but will be mandatory if a primary breast lesion is not evaluable by ultrasound, or if there are signs of disease progression on the Week 9 ultrasound (see Figure 6).

Breast MRI scans should not be acquired within 48 hours after biopsy, and the 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 as assessed by the central reading facility, the scan may be repeated, at least 48 hours after the first scan before the start of study treatment. Other MRI acquisition sequences, such as diffusion-weighted imaging, may be acquired during this study during the MRI scan visits for each patient. Additional MRI-derived metrics such as ADC value may provide additional insight into changes in tumor cellular composition.

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

### 4.5.8 Surgical Treatment Plan

The planned and actual surgical treatment (BCS or mastectomy) performed should be documented and reported in the eCRF. Patients should be reassessed after completion of neoadjuvant therapy and prior to surgery.

### 4.5.9 Surgical Specimen – Pathology

The co-primary endpoint of the study (pCR) will be as identified by local pathology review. Guidelines regarding pathology specimen preparation, labeling and review are outlined in the pathology manual.

### 4.5.10 Laboratory Assessments

The following assessments will be performed at the local laboratory. The frequency of assessments is provided in Appendix 1.

- Hematology (complete blood count, including red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with differential [neutrophils, eosinophils, basophils, lymphocytes, monocytes, and other cells]), and platelet count.
- Coagulation (INR and aPTT/PTT)
- Fasting serum chemistry (blood urea nitrogen [BUN], creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, ALT), performed following $\geq$10-hour fast
- Fasting lipid profile and amylase (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides, amylase, and lipase) performed following a $\geq$10 hour fast
- Fasting insulin and glucose
- Glycosylated hemoglobin ($HbA_{1c}$)

- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)

The following assessments will be performed at a central laboratory. Instruction manuals outlining sampling procedures, storage conditions, and shipment instructions and supply kits will be provided for all central laboratory assessments:

- Mandatory tumor tissue
- 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 *PIK3CA* mutation testing as well as for other protocol-mandated exploratory assessments at baseline, Day 15, and at surgery.
- Tumor tissue should be of good quality based on total and viable tumor content. Evaluation of the patient's tumor sample for adequate tumor tissue content by a central laboratory must occur prior to initiation of study treatment. A minimum of ten unstained slides from a prior diagnostic FFPE core biopsy would be required for enrollment eligibility purposes.

  Two formalin-fixed, paraffin-embedded core needle biopsies and one freshly frozen OCT core needle biopsy are required at baseline and Day 15 (Week 3).

  A formalin-fixed, paraffin-embedded tumor block from surgical resection (Weeks 17 – 18) is required. If a tumor block cannot be obtained for various reasons (e.g., the tumor tissue is not sufficient at surgical resection), the site should discuss with the central study team. In such cases, paraffin-embedded, unstained slides (a minimum of 20 and up to 40 unstained slides) from a surgical specimen are required at surgery (Weeks 17 – 18).

  The specimens will be used for confirmatory central laboratory assessment of *PIK3CA* mutation status, Ki67, PTEN, ER/PgR and HER2 expression. In addition, other exploratory assessments, including but not limited to, PI3K signaling pathways may be evaluated, including protein expression and molecular profiling studies such as NGS and gene-expression.
- Plasma samples for exploratory research on candidate biomarkers include, but are not limited, to the following: ctDNA and plasma protein biomarkers
- Blood for NGS (if approved by local regulatory authorities)
- Blood for pharmacogenomics (if approved by local regulatory authorities)
- PK assessment

  Plasma samples will be collected to measure letrozole and GDC-0032 concentrations (see 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.

### 4.5.11 Assay Methods

#### 4.5.11.1 Mutational Analysis for *PIK3CA*

The *PIK3CA* mutation assay will be performed by a central laboratory.

Somatic mutations in the *PIK3CA* gene are found in approximately 35%−40% of ER-positive breast cancers and occur most commonly in Exons 9 and 20 in the codons encoding amino acids E542, E545, and H1047 (Saal et al. 2005). Real-time polymerase chain reaction (RT-PCR) assays that amplify exons that are commonly mutated in *PIK3CA* offer a sensitive and quantitative method to detect mutations from a tumor specimen. DNA will be extracted from tumor samples and subjected to allele-specific PCR assays that detect the WT allele, as well as to assays for nucleotide substitutions that include, but are not limited to, the following amino acid changes: R88Q, N345K, C420R, E542K, E545K/A/G/D, E546K/E/R/L, M1043I, H1047R/L/Y, H1049R. Following histopathological review, samples with $<$10% tumor content may not be evaluable for the *PIK3CA* assay. Samples will be run on cobas z480 analyzer, and *PIK3CA* mutation status (mutant or WT) will be made using appropriate cutoffs and automated software.

A designation of *PIK3CA* status unknown will be assigned to a sample wherein any one of the predefined mutations was not conclusively assessed.

#### 4.5.11.2 Pharmacodynamic Biomarker Assays in Tumor Tissues

Ki67 antigen is an important cell cycle-related nuclear protein that is expressed by proliferating cells in all phases of the active cell cycle (G1, S, G2, and M phase). As such, it is a useful marker of the proliferative state of a tumor. Ki67 protein levels will be determined by IHC through the use of standard techniques.

PI3K pathway, and other pro-survival, biomarkers will be tested in the fresh tumor biopsies by IHC, including, but not limited to, phospho-S6, phospho-AKT, phospho-4EBP1, and phospho-ERK. If tissue quantity permits, change in expression of pathway biomarkers will be measured by the RPPA using OCT fixed tissue. The basis of the technology is to immobilize small amounts of lysate from a tumor biopsy sample in serial dilution on a microarray slide. Multiple samples are thus arrayed on a slide and can be probed with antibodies that detect a particular phospho-epitope. Using this technology, we will profile approximately 80 key signaling nodes representing a number of pathways known to be dysregulated in cancer, including receptors in the HER family, multiple components of PI3K/mTor signaling, as well as key members of the RAS/MAP kinase pathway.

#### 4.5.11.3 Analysis of Phosphatase Tensin Homolog Expression

PTEN status will be examined by IHC using a protocol that has been validated for specificity using several available cell line controls at a central laboratory. Tumor specimen will be scored only if appropriate staining is observed in internal control stromal or normal (non-tumor) tissue elements.

#### 4.5.11.4 Confirmation of Estrogen Receptor, Progesterone Receptor, and HER2 Status

ER, PR, and HER2 status will be determined at a central laboratory according to the American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) guidelines.

#### 4.5.11.5 Circulating Tumor DNA Analysis

ctDNA will be extracted from plasma samples collected from patients and used for the detection of oncogenic mutations using appropriate technologies. The prevalence of the mutations measured at baseline and post-treatment may provide information on response or resistance to therapy.

#### 4.5.11.6 Messenger RNA Expression Profiling

In cases where there is sufficient archival tissue to isolate RNA, gene expression will be performed using gene expression assays conducted on the NanoString platform or equivalent. Analysis may include, but is not limited to, a panel of genes important for intrinsic subtyping, breast cancer biology and PI3K signaling. The goal will be to generate a database of expression status to examine whether there are gene expression patterns that are associated with clinical response to GDC-0032.

#### 4.5.11.7 Next Generation Sequencing

In cases where there is sufficient material to isolate DNA, NGS will be performed using NGS platforms, such as Illumina or equivalent. The goal will be to determine whether the percentage of genetic mutations are associated with clinical response to GDC-0032.

#### 4.5.11.8 Copy Number Analysis

The level of copy number alterations in cancer-related genes may be determined using DNA-based technologies, either cytogenetically using chromosomal in situ hybridization (ISH), using next-generation sequencing platforms or by RT-PCR-based or equivalent technologies. For cytogenetic assays, detection may be either fluorescence-based (fluorescence in situ hybridization assay) or chromogenic-based (chromogenic in situ hybridization). Increased copy number of PI3K pathways activating genes may provide information on response or resistance to therapy.

#### 4.5.11.9 Plasma Biomarker Analyses

Assays to assess the expression of soluble, systemic cytokines, and chemokines from the plasma of patients will be carried out using appropriate methodologies, such as enzyme-linked immunosorbent assay (ELISA)-based or mass spectrometry-based or equivalent technologies.

#### 4.5.11.10 Plasma Pharmacokinetic Samples

Plasma GDC-0032 and letrozole samples will be analyzed using a validated liquid chromatography tandem mass spectrometry.

After the plasma samples are analyzed, any remaining samples may be used for exploratory metabolite profiling and identification, ex vivo protein binding, and PK, or pharmacodynamic assay development purposes.

#### 4.5.11.11 Pharmacogenetic Polymorphism Assay

If approved by the local regulatory authority, gene mutations will be assayed using multiplex PCR, allele-specific PCR, direct sequencing, or other acceptable methods. Results may be correlated to population PK parameters or other clinical measures in order to better understand the impact of genetic variants on drug metabolism, exposure, adverse events, and/or response.

A sample will also be utilized as a source of normal DNA to determine whether sequence variants in the *PIK3CA* gene and in other relevant oncogenes in the tumor DNA are somatic mutations or single nucleotide polymorphisms.

#### 4.5.11.12 Electrocardiograms

Triplicate ECG recordings will be obtained at each specified timepoint (see the schedule of assessments in Appendix 1).

#### 4.5.11.13 DLCO Testing

A diffusion capacity of the lung for carbon monoxide (DLCO) test will be required at baseline and at the end of study-drug treatment (prior to surgery) for all patients. The DLCO test should be repeated if there is clinical suspicion of pneumonitis. Further guidance regarding DLCO testing is contained in Appendix 7 and in the management guidelines for pneumonitis (Section 5.1.1.2).

#### 4.5.11.14 Osteoporosis Assessment and Monitoring

Treatment with aromatase inhibitors results in bone loss due to estrogen deficiency *(Gaillard and Stearns 2011)*. For patients who have a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis, a bone mineral density assessment will be required at baseline prior to initiating study treatment. Baseline bone mineral density will be measured via dual-energy X-ray absorptiometry (DXA). DXA measurement of both the hip and lumbar spine is suggested. When either the hip or lumbar spine is not a valid skeletal site for a bone mineral density measurement, then the 33% (one-third) radius should be measured. In some patients, measurement of the hip alone could be sufficient.

Appropriate monitoring in these patients will occur per institutional guidelines. Assessment for fractures is already included as part of the scheduled physical examinations. Determination of patients who are at increased risk for osteoporosis will be per institutional guidelines. Clinical risk factors for fracture include advancing age, previous fracture, glucocorticoid therapy, parental history of hip fracture, low body weight, current cigarette smoking, excessive alcohol consumption, rheumatoid arthritis, and *conditions predisposing to* secondary osteoporosis (e.g., hypogonadism or premature

menopause, malabsorption, chronic liver disease, inflammatory bowel disease) (Kanis et al. 2005).

### 4.5.12 Patient-Reported Outcomes

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of GDC-0032. The PRO questionnaires, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

The EORTC QLQ-C30 and the Modified Breast Cancer module QLQ-BR23 questionnaires will be used to assess HRQoL, including side-effects of systemic therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems) and patient functioning during the neoadjuvant period (refer to schedule of assessments in Appendix 1 for a detailed description of timepoints) and post-surgery follow-up.

The EORTC QLQ-C30 is a widely used HRQoL measure in oncology trials with excellent psychometric properties demonstrating both reliability and validity. The measure consists of “five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale” with a recall period of “the past week” (Aaronson et al. 1993). Scale scores can be obtained for each of the multi-item scales, global health status/QoL scale, and six single items by using a liner transformation for standardization of the calculated raw score.

The EORTC QLQ-BR23 breast cancer module was first validated for use in 1995, uses a recall period of “the past week,” and is intended for use across multiple treatment modalities (i.e., surgery, chemotherapy, radiotherapy, and hormonal treatment). As this trial will include patients in the neo-adjuvant setting, the last seven items of the original BR23 questionnaire, items numbered 47 – 53 that deal with symptoms and side effects not relevant to the population under study, will be removed. These seven items addressed symptoms experienced by metastatic breast cancer patients and those undergoing radiation. Therefore, in consultation with the EORTC, these items were deleted, as the validity of the measure would not be compromised by their removal. In addition, as “oral mucositis” and “skin problems” are key symptoms of this therapy not assessed by currently available tools, validated items from the EORTC item bank were added to assess the presence and bothersomeness of oral mucositis (2 items: sore mouth/tongue, difficulty swallowing) and skin problems (2 items). Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results. Scale scores can be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score.

The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. Patients must complete these instruments in the clinic (cannot be taken home) prior to any healthcare provider interactions (i.e., prior to administration of study drug and prior to any other study assessment) to ensure that the validity of the instruments are not compromised and to ensure that data quality meet regulatory requirements.

Refer to Appendix 4 for the EORTC QLQ-C30 and the modified QLQ-BR23.

### 4.5.13 Samples for Clinical Repository

All residual samples (or leftover biologic samples after protocol-defined studies are completed) obtained during the study (FFPE, fresh-frozen, plasma, etc.) will be stored in an academic central repository. The specimens in the study repository will be made available for future biomarker research towards further understanding of treatment with GDC-0032, of breast cancer, related diseases, and adverse events, and for the development of potential, associated diagnostic assays. The implementation of study repository specimens is governed by the Study Steering Committee, with guidance from a dedicated Translational Research Committee to ensure the appropriate use of the study specimens.

All biomarker specimens will be retained for new research related to this study and/or disease in accordance with the recommendations and approval of the Study Steering Committee. Samples will be only destroyed if required by local laws relating to the collection, storage, and destruction of biological specimens.

Specimens will be stored up to 15 years or until they are exhausted. The storage period will be in accordance with the institutional review board/ethics committee (IRB/EC)-approved ICF and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

#### 4.5.13.1 Confidentiality

Patient medical information associated with biologic specimens is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from biologic specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using biologic specimens will be available in accordance with the effective Translational Reseach Committee policy on study data publication.

## 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

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.

### 4.6.2 Study Treatment Discontinuation

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

- Pregnancy
- Disease progression
- Unacceptable toxicity

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 Conditions for Terminating the Study

Both the Sponsor and the investigator reserve the right to terminate their participation in the study under the circumstances agreed upon in the site agreement. Should this be necessary, both parties will arrange the procedures on an individual basis after review and consultation. In terminating the study, the Sponsor and investigator will assure that adequate consideration is given to the protection of the patients' interest.

# 5. ASSESSMENT OF SAFETY

## 5.1 SAFETY PLAN

GDC-0032 is not approved and is currently in early clinical development. Thus, the entire safety profile is not known at this time. Human experience is currently limited. The following information is based on results from ongoing clinical studies. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events, and laboratory abnormalities (see Section 5.3.5.3), defined and graded according to NCI CTCAE v4.0. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistry and blood counts. All serious adverse events and non-serious adverse events of special interest will be reported in an expedited fashion, via fax to Austrian Breast and Colorectal Cancer Study Group (ABCSG) safety department and also captured in the electronic data capture (EDC) system. In addition, the Sponsor and the investigators will review and evaluate observed adverse events on a regular basis.

All adverse events will be recorded during the trial and for 30 days after the last dose of study treatment or until the end of study visit, whichever occurs later. Patients who have an ongoing study treatment-related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

All adverse events should be attributed by the investigator to study drug or to another clearly identified etiology by the investigator (see Table 9).

Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections.

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

### 5.1.1 Management of Specific Adverse Events of GDC-0032

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

Due to the approximately 40-hour half-life for GDC-0032, investigators should consider holding GDC-0032 for certain Grade 2 toxicities until the adverse event resolves to Grade ≤ 1 as discussed below (e.g., stomatitis/mucositis, colitis, rash, diarrhea, pneumonitis). Certain toxicities can occur within 1–2 weeks of holding or discontinuing GDC-0032 drug (e.g., pneumonitis, colitis, rash). In these cases, the adverse event eventually resolves. Investigators should follow management guidelines and dose modifications for toxicities as described below, including administration of topical or systemic corticosteroids as appropriate.

**Table 1 Overall Dose Modification Guideline for GDC−0032-Related Adverse Events**

| | GDC-0032 |
|---|---|
| Starting dose | 4 mg at 5 days on / 2 days off |
| First reduction | 2 mg at 5 days on / 2 days off |
| Second reduction | 2 mg at 3 days on / 4 days off [a] |

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

#### 5.1.1.1 Management of Hyperglycemia

Metformin is the first antihyperglycemic medication of choice because of the lower risk of hypoglycemia with this agent. Because metformin in some patients may also cause diarrhea and not be well tolerated, other antihyperglycemic medications such as sulfonylureas (e.g., glimepiride, glipizide) can be used. Extra caution should be used with other drugs such as sulfonylureas because of the increased risk for hypoglycemia with these agents. Consultation with an endocrinologist can be helpful in managing hyperglycemia.

Specific dose modification and management guidelines for hyperglycemia are provided in Table 2.

**Table 2 Dose Modification and Management Guidelines for Hyperglycemia (Based on Fasting Blood Glucose)**

| Grade | Dose Modification and Management Guidelines for Hyperglycemia (based on fasting blood glucose) |
|---|---|
| Grade 2 | Initiation of an anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring will be implemented.<br>Dosing with GDC-0032 may either be held or continued per investigator evaluation. |
| Grade 3 (asymptomatic) | GDC-0032 dosing will be suspended and the patient will be managed as per standard of care, including implementation of additional glucose monitoring and initiation of, or an increase in, the dose of an anti-hyperglycemic therapy (e.g., metformin).<br>If the hyperglycemic event does not improve to Grade ≤ 1 within 28 days, GDC-0032 will be permanently discontinued.<br>If the hyperglycemic event improves to Grade ≤ 1 within 28 days, GDC-0032 dosing may resume at one dose level lower, with approval by the Medical Monitor. |

**Table 2 Dose Modification and Management Guidelines for Hyperglycemia (Based on Fasting Blood Glucose) (cont.)**

| | |
|---|---|
| Grade 3 (symptomatic) [a], Grade 3 (requiring hospitalization), or Grade 4 | GDC-0032 dosing will be suspended, and the patient will be managed as per standard of care, including implementation of additional glucose monitoring and initiation of, or an increase in, the dose of anti-hyperglycemic therapy.<br>If the hyperglycemic event does not improve to Grade ≤ 1 within 28 days, GDC-0032 will be permanently discontinued.<br>If the hyperglycemic event improves to Grade ≤ 1 within 28 days, GDC-0032 dosing may resume at one dose level lower, with approval by the Medical Monitor. |

[a] For example, blurred vision, frequent urination, excessive thirst.

#### 5.1.1.2 Management of Pneumonitis

Patients who require any daily supplemental oxygen are not eligible for the study. Patients who have DLCO values < 60% will be excluded from the study. Patients will be assessed for pulmonary signs and symptoms throughout the study. The DLCO test should be repeated if there is clinical suspicion of pneumonitis. The DLCO test will also be repeated presurgery after completion of study treatment. Management guidelines for patients with possible pneumonitis are listed in Table 3.

**Table 3 Dose Modification and Management Guidelines for Pneumonitis**

| Grade | Intervention | Investigations | GDC-0032 [a] Dose Adjustment |
|---|---|---|---|
| 1 | No specific therapy required. | CT scan. Consider DLCO. [b] Repeat CT scan every 8 weeks until return to baseline. | No change. |
| 2 | Symptomatic only. Prescribe corticosteroids if cough is troublesome. | CT scan. Repeat CT scan and DLCO every 4 weeks until return to baseline. Consider bronchoscopy. | *Interrupt GDC-0032 treatment* until improvement to Grade ≤ 1. Interrupt treatment as long as corticosteroids are being given.<br>Restart GDC-0032 at the same dose if clinical benefit evident. Consider restarting at reduced dose if recurrent event or per discussion with Medical Monitor.<br>Discontinue treatment if recovery to Grade ≤ 1 is not evident within 28 days. |

**Table 3 Dose Modification and Management Guidelines for Pneumonitis (cont.)**

| | | | |
|---|---|---|---|
| 3 | Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated. | CT scan. Repeat CT scan and DLCO every 4 weeks until return to baseline. [c] Bronchoscopy is recommended. | Interrupt treatment until improvement to Grade ≤ 1.<br>Restart therapy within 28 days at a reduced dose if clinical benefit is evident.<br>Interrupt treatment as long as corticosteroids are being given. |
| 4 | Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated. | CT scan. Repeat CT scan and DLCO every 4 weeks until return to baseline. Bronchoscopy is recommended. | *Permanently discontinue GDC-0032.* |

Table modified from White et al. 2010.

CT = computed tomography; DLCO = diffusion capacity of the lung for carbon monoxide.

[a] Dose reductions per Section 5.1.1.

[b] DLCO may be useful to monitor the effect of interventions such as dose reduction/discontinuation and corticosteroids, in conjunction with imaging (White et al. 2010).

[c] *Follow-up imaging and investigation should be coordinated with the local pulmonologist if no baseline scans are available.*

#### 5.1.1.3 Management of Rash

Rash and other dermatological events should be closely monitored, and patients with severe rash should be monitored for associated signs and symptoms such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. For severe rash, dosing of GDC-0032 should be interrupted, and patients should be treated with supportive therapy per standard of care. Use of antihistamines, as well as topical or systemic corticosteroids, may be considered (see Table 4).

**Table 4 GDC-0032 Dose Modification and Management Guidelines for Rash**

| Grade of Rash | GDC-0032 |
|---|---|
| Grade 1 | Continue dosing at current dose and monitor for change in severity.<br>Consider prescribing topical corticosteroids [a] |
| Grade 2 | Consider holding GDC-0032 or reducing to the next lower dose if rash is troublesome.<br>Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]). |
| Grade 3 | Hold GDC-0032 until Grade ≤ 1.<br>Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]).<br>Consider dermatological consultation.<br>Consider obtaining photographs of rash if permitted by local regulations.<br>After rash improves to Grade ≤ 1, restart GDC-0032 at the next lower dose upon discussion with Medical Monitor, or permanently discontinue. |
| *Grade 4* | *Permanently discontinue GDC-0032.* |

AE = adverse event.

AE grading is based on NCI CTCAE, Version 4.0.

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

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

#### 5.1.1.4 Management of Gastrointestinal Toxicity

##### 5.1.1.4.1 Management of Diarrhea *and Colitis*

Patients should be closely monitored for gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain, stomatitis, and changes in stool, including checking for blood in stool if clinically indicated). Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. Gastrointestinal symptoms should be managed per protocol guidelines and institutional standard of care. For example, prompt management of diarrhea with antidiarrheal medications should be implemented. Because of the approximately 40-hour half-life of GDC-0032, investigators should hold GDC-0032 for Grade ≥ 2 diarrhea.

*Steroid-responsive diarrhea and colitis have been difficult to distinguish in patients treated with GDC-0032. All cases of colitis have been reversible with corticosteroid treatment. Prompt initiation of corticosteroids for persistent diarrhea despite antidiarrheal treatment can decrease the severity of the diarrhea and prevent the need for hospitalizations. Patients who develop severe steroid-responsive diarrhea usually have been on GDC-0032 treatment for at least 2 months, with an average onset between 4 – 6 months of treatment. A stool culture is helpful in identifying concurrent*

*infections, and patients have been successfully treated with concurrent steroids and appropriate antibiotics if needed.*

*If a patient is being treated with corticosteroids, total parenteral nutrition is discouraged as this increases the risk for severe hyperglycemia. Discontinuation of nonsteroidal inflammatory medications or other medications that exacerbate colitis are also recommended during colitis episodes.*

*Perforated duodenal ulcer has been observed in 2 patients (one patient at 6 mg in combination with letrozole; another patient at 6mg in combination with fulvestrant). Appropriate caution should be taken with the administration of medications such as aspirin, nonsteroidal anti-inflammatory drugs, and corticosteroids, which can increase the risk of gastritis, peptic ulcers, or gastrointestinal perforation.*

Specific dose modification and management guidelines for diarrhea *and colitis* are provided in Table 5.

**Table 5 GDC-0032 Dose Modification and Management Guidelines for Diarrhea *and Colitis***

| Grade of Diarrhea | Dose Modification and Management Guidelines |
|---|---|
| Grade 1 | • Manage per institutional standard of care that includes antidiarrheals.[a]<br>• *For persistent Grade 1 diarrhea occurring after Cycle 2, recommend evaluation for infectious causes via stool culture.[b] For noninfectious diarrhea, consider colonoscopy to evaluate for colitis.* |
| Grade 2 | • Hold GDC-0032 and *initially* manage *with* antidiarrheals.[a]<br>• *Obtain stool culture for infectious workup.[b] Infections (e.g., Clostridium difficile, enteric bacteria, CMV) should be treated with the appropriate antibiotic.*<br>• For persistent Grade 2 non-infectious diarrhea *lasting longer than 48 hours* despite treatment with antidiarrheals*, treat with oral* corticosteroids *(20 –40 mg prednisone QD starting dose with taper) or* budesonide *9 mg PO QD.*<br>• *If* Grade 2 diarrhea *occurred after Cycle 2, was a* recurrent *episode, or improved with corticosteroid treatment, resume GDC-0032 treatment at one dose level lower upon improvement to Grade ≤ 1 and after completion of corticosteroid treatment.*<br>• *If* Grade 2 diarrhea *occurred before Cycle 2, did not require corticosteroid treatment, and was an initial episode, resume GDC-0032 treatment* at the *same dose upon improvement to Grade ≤ 1.*<br>• *For Grade 2 colitis, resume GDC-0032 treatment at one dose level lower upon improvement to Grade ≤ 1 and after completion of corticosteroid treatment.* |

| Grade of Diarrhea | Dose Modification and Management Guidelines |
|---|---|
| | • *If Grade 2* diarrhea *does not improve after 48 hours of corticosteroid treatment, a colonoscopy is recommended to evaluate for other causes of diarrhea (e.g., CMV colitis).* |
| Grade 3 *(first episode)* | • Hold GDC-0032 and *initially with* antidiarrheals.[a]<br>• *Obtain stool culture for infectious workup.*[b]<br>• *For G3 diarrhea or colitis, treat with systemic corticosteroids (prednisone 60 –80 mg QD equivalent or solumedrol 16 –20 mg IV q8hr to start). Can increase steroid dosage if diarrhea does not improve.*<br>• *Concurrent infections (e.g., Clostridium difficile, enteric bacteria, CMV) should be treated with the appropriate antibiotic.*<br>• *For patients who do not improve upon 48 hours of corticosteroid treatment, a colonoscopy is recommended to evaluate for other causes of diarrhea (e.g., CMV colitis).*<br>• *If diarrhea or colitis improves to Grade ≤ 1 and upon completion of any steroid taper or antibiotic treatment, resume GDC-0032 treatment at one dose level lower.* |
| *Grade 3 (recurrent) or Grade 4* | • *Permanently discontinue GDC-0032.*<br>• *Workup and treatment algorithm as for Grade 3 (first episode).*<br>• *If patient receiving endocrine therapy, upon recovery to Grade ≤ 1, can resume endocrine therapy alone.* |

*CMV =cytomegalovirus; IV =intravenous; PO =oral; QD =once daily; q8hr =every eight hours; SOC =standard of care.*

[a] *Suggested antidiarrheals include the following: loperamide (initial: 4 mg, followed by 2 mg after each loose stool, up to 16 mg/day); diphenoxylate and atropine (Diphenoxylate 5 mg 4 times/day until control achieved [maximum: 20 mg/day], then reduce dose as needed; some patients may be controlled on doses of 5 mg/day; tincture of opium (6 mg of undiluted opium tincture [10 mg/mL]) 4 times daily.*

[b] *Non-infectious diarrhea can be diagnosed by stool culture with workup for various enteric bacteria and C. difficile. Fecal calprotectin is a possible marker for bowel inflammation. Blood-based CMV PCR test can also be used to detect CMV infection.*

#### 5.1.1.4.2 Management of Stomatitis and Oral Mucositis

Aggressive mouth care for oral mucositis and stomatitis with mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) may also be helpful in managing symptoms, and it is recommended that these are implemented with early signs of dry mouth, Grade 1 mucositis, or Grade 1 stomatitis (see Table 6). Avoidance of spicy foods may also be helpful.

**Table 6 GDC-0032 Dose Delay and Modification Guidelines for Stomatitis and Oral Mucositis**

| Grade of Stomatitis/Mucositis | GDC-0032 |
|---|---|
| All grades | • Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics)<br>• Diet management (e.g., avoidance of spicy foods) |
| Grade 1 | • Monitor symptoms and initiate management (see above). Re-evaluate within 48 – 72 hours. |
| Grade 2 | • Hold GDC-0032 and manage until Grade ≤ 1.<br>• Restart GDC-0032 at the same dose.<br>• If Grade 2 stomatitis/oral mucositis recurs, hold GDC-0032 until Grade ≤ 1. Restart GDC-0032 at the next lower dose. |
| Grade 3 | • Hold GDC-0032 and manage until Grade ≤ 1. Restart GDC-0032 at the next lower dose.<br>For Grade 3 event that was not adequately managed upon initial presentation, consider restarting at same dose upon discussion with Medical Monitor. |
| *Grade 4* | • *Permanently discontinue GDC-0032.* |

### 5.1.2 *Management of Abnormal Liver Function Tests*

*Some patients have experienced elevations of liver function tests (e.g., AST or ALT). Patients will be monitored throughout the study treatment for changes in liver function tests. Given the potential for hepatic toxicity, all patients must have adequate liver function as manifested by measurements of serum bilirubin, hepatic transaminases, and alkaline phosphatase for initial and continued dosing. Separate criteria for eligibility, continued dosing, and DLT are given for patients with hepatic metastases and Grade 2 hepatic transaminase and/or alkaline phosphatase levels at baseline to allow safety testing to be adequately assessed in this patient group.*

*For new abnormal liver function tests (e.g., elevated AST or ALT), a standard clinical work-up to understand the etiology of the abnormality should take place per local guidelines. In many cases, elevated liver function tests may be a result of liver metastases, concomitant medications, or biliary obstruction. Dose modifications for elevated liver function tests are described in Table 7.*

### 5.1.3 *Management of Asymptomatic Lipase and/or Amylase Elevations*

*Some patients treated with GDC-0032 have experienced asymptomatic lipase and/or amylase elevations in blood tests without any clinical or radiographic symptoms of pancreatitis or another clear etiology for the abnormal laboratory values. Upon discussion with the Medical Monitor and after a risk-benefit assessment, investigators*

*can consider continuing GDC-0032 therapy in such patients at the same dose or one dose level lower. Investigators should have a low threshold for interrupting GDC-0032 for any concerning clinical gastrointestinal toxicities.*

### 5.1.4 Management of Other Clinically Significant Adverse Events

See Table 7 for the dose modifications for other clinically significant adverse events.

**Table 7 GDC-0032 Dose Delay and Modification Guidelines for Other Clinically Significant Adverse Events**

| Grade | GDC-0032 |
|---|---|
| Grade 3: first event | • Hold GDC-0032 until Grade ≤ 1.<br>• Consider restarting at next lower dose. |
| Grade 3: recurrent<br>Grade 4: non-life-threatening | • Hold GDC-0032 until Grade ≤ 1.<br>• Restart at next lower dose. |
| Grade 4: life-threatening | • Permanently discontinue GDC-0032. |

### 5.1.5 General Guidance for Dose Modifications and Delays for Letrozole

The letrozole dose level cannot be modified. In general, the investigator can consider continuing letrozole if it is not thought to be letrozole-related.

All dose modifications should be based on the adverse event requiring the greatest modification and should be properly documented in the source documents.

### 5.1.6 Management of Increases in QT Interval

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

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

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

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

In rare circumstances, it may be acceptable to resume study drug, at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

### 5.1.7 Safety Monitoring for Letrozole

Letrozole is a nonsteroidal AI indicated for first line treatment of hormone receptor positive, locally advanced, or metastatic breast cancer in postmenopausal women. Letrozole is also indicated for adjuvant treatment in postmenopausal hormone-receptor positive patients and for the treatment of advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

The most frequently reported adverse events in a first line, breast cancer clinical trial with letrozole were bone pain, hot flushes, back pain, nausea, arthralgia, and dyspnea. Clinically significant adverse events also include bone effects (osteoporosis and bone fractures) and hypercholesterolemia. Discontinuations for adverse events other than progression of tumor occurred in 2% of patients on letrozole. Refer to the U.S. letrozole Package Insert or SmPC for additional information.

There are no expected significant overlapping toxicities between letrozole and GDC-0032. Routine safety monitoring and periodic laboratory tests for the letrozole and GDC-0032 combination will occur throughout the study.

## 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; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and 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 ABCSG)

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

- Fatal (i.e., the adverse event actually causes or leads to death)
- 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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 (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 ABCSG safety department 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 ABCSG)

Non-serious adverse events of special interest are required to be reported by the investigator to ABCSG safety department 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:

- Grade 4 hyperglycemia
- Grade $\geq$ 3 symptomatic hyperglycemia
- Grade $\geq$ 2 colitis or enterocolitis
- Grade $\geq$ 3 diarrhea
- Grade $\geq$ 3 rash
- Grade $\geq$ 2 pneumonitis
- 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 5.3.5.5)
- Suspected transmission of an infectious agent by the study drug

## 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 additionally reported to ABCSG safety department in case they fulfill the criteria for expedited reported in accordance with instructions provided in this section and in Section 5.4 –Section 5.6.

For each adverse event recorded on the Adverse Event CRF, 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

**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 until the end of study visit, whichever occurs later. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern deemed related to prior study drug treatment or study procedures (Section 5.6).

### 5.3.2 Eliciting Adverse Event Information

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

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

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

### 5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 4.0) will be used for assessing adverse event severity. Table 8 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 8 Adverse Event Severity Grading Scale**

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

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

Note: Based on the most recent version of NCI CTCAE (v 4.0), 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 one's self, 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 9):

- 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 (where 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 9 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 | Adverse events will be considered related, unless they fulfill the criteria as specified below.<br>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.

If known, a diagnosis 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.

#### 5.3.5.1 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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.

#### 5.3.5.2 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. The progression (increase and decrease) of an adverse event must be documented in the Adverse Event eCRF.

The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

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

#### 5.3.5.3 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:

- 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
- Clinically significant in the investigator's judgment

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 the 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

#### 5.3.5.4 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:

- 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
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

#### 5.3.5.5 *Reporting of* Abnormal Liver Function Tests *as Hy's Law*

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × 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 ABCSG safety department immediately (i.e., no more than 24 hours after learning of the event), either as serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

#### 5.3.5.6 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 ABCSG safety department (see Section 5.4.2). This includes death attributed to progression of breast cancer.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used 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 of 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.

#### 5.3.5.7 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 *e*CRF.

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”).

#### 5.3.5.8 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:

- Perform an efficacy measurement for the study
- Hospitalization for respite care
- Planned hospitalization required by the protocol for breast cancer surgery
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
    - The patient has not suffered an adverse event
- Hospitalization due solely to progression of the underlying cancer
- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care
- Hospitalization for protocol mandated biopsies

#### 5.3.5.9 Adverse Events Associated with an Overdose

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 serious criteria, the event should be reported to the ABCSG safety department immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

### 5.3.5.10 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO ABCSG

Certain events require immediate reporting to allow ABCSG safety department to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to ABCSG safety department 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 ABCSG safety department 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 ABCSG safety department 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

**U.S. Medical Monitor Contact Information**

Genentech's Medical Monitor Contact Information:

Medical Monitor: [redacted], M.D., Ph.D.

Telephone No.

Alternate Telephone No.: [redacted]

**Medical Monitor Contact Information for Sites outside the United States:**
Please refer to the country/region-specific phone numbers provided in the study binder.

### 5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the paper Serious Adverse Event reporting form and transmit to ABCSG safety department via fax. In addition the serious adverse event and non-serious adverse event of special interest information will be captured in the EDC system.

| | |
|---|---|
| Worldwide Sites: | ABCSG safety department |
| Fax No.: | +43 1 409 09 90 |

Relevant follow-up information should be submitted to ABCSG safety department as soon as it becomes available and/or upon request.

## 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 (SDV). For follow-up reports of serious adverse events and non-serious adverse events of special interest, investigators should record all follow up information immediately (i.e., within 24 hours) on the paper Serious Adverse Event reporting form and transmit to ABCSG safety department via fax. In addition the serious adverse event and non-serious adverse event of special interest follow-up information will be captured in the EDC system. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF and paper Serious Adverse Event form, if applicable.

All pregnancies reported during the study should be followed until pregnancy outcome, and they should be reported according to the instructions provided in Section 5.4.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor and/or ABCSG safety department 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

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

*The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (30 days after the last dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death, other serious adverse event, or non-serious adverse event of special interest occurring after the end of the adverse event reporting period, regardless of causality. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug or the female partner of a male patient exposed to study drug.*

*The investigator should report these events by completing and faxing a paper Serious Adverse Event Reporting Form and fax cover sheet to Safety Risk Management using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of 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:

- GDC-0032 Investigator's Brochure
- Local prescribing information for letrozole SmPC

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.

An IDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Primary and secondary efficacy analyses will include all patients who were included in the randomization. Final analysis will be performed after last patient, last visit (LPLV) and subsequent data cleaning, with patients allocated to the treatment arm associated by randomization.

Safety analyses will include all patients who were included in the randomization and received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

## 6.1 DETERMINATION OF SAMPLE SIZE

This study is designed for testing the effect of GDC-0032 on the two co-primary endpoints in all enrolled patients and in the *PIK3CA* MT patients and plans to enroll 330 patients in total. Assuming the *PIK3CA* mutation status will not be available (unknown) for approximately 10% of the patients and the prevalence of *PIK3CA* mutant is 40%, there will be approximately 120 patients in the *PIK3CA* MT cohort.

Given that the *PIK3CA* mutation status is not a stratification factor for randomization, there might be a possible imbalance between treatment arms within the *PIK3CA* MT cohort, which may reduce the statistical power in this cohort. To ensure the study provides sufficient statistical power even when the treatment assignment is imbalanced, the sample size was calculated based on a conservative scenario by assuming that the treatment assignment imbalance in *PIK3CA* MT is 40% vs. 60%. The sample size was calculated based on a chi²-test using continuity correction (Ury and Fleiss 1980).

To control an overall, two-sided, family-wise error rate under 20%, we use a two-sided significance level of 16% and 4% for the co-primary endpoints MRI ORR, and pCR, respectively.

Assuming 10% of the patients are unevaluable for the MRI ORR, approximately 300 enrolled patients and 108 patients in the *PIK3CA* MT cohort will be evaluable for analyses. This sample size allows us to detect an absolute percentage increase of 24% in MRI ORR rate in the GDC-0032 plus letrozole arm (64%) versus the letrozole-only arm (40%; Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at 80% power and 16% two-sided significance level. The minimal detectable difference for ORR is approximately 15%.

Assuming that all patients are evaluable for pCR (i.e., approximately 330 enrolled patients and 120 in the *PIK3CA* MT cohort), this sample size provides 80% power to

detect an absolute percentage increase of 18% in pCR in the GDC-0032 plus letrozole arm (19%) versus the letrozole-only arm (1%, Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at the 4% two-sided significance level. The minimal detectable difference for pCR rate is approximately 13%.

If the prevalence of the *PIK3CA* mutation is lower than assumed, if there is more substantial treatment assignment imbalance in the *PIK3CA* MT cohort than assumed, or there is an increased number of unevaluable patients for the MRI ORR, the sample size may be increased to obtain the level of power at 80%, and the enrollment may be limited to patients with *PIK3CA* MT.

## 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 incidence of study treatment discontinuation for reasons other than disease progression will be tabulated.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables, stratification factors, and other baseline characteristics will be summarized by treatment arm.

## 6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include the ITT population; that is, all randomized patients will be included in the analyses, with patients grouped according to the treatment assigned at randomization.

### 6.4.1 Primary Efficacy Endpoint

The co-primary efficacy endpoints are (1) tumor ORR, assessed by modified RECIST criteria by breast MRI *(centrally assessed)* and (2) the rate of pCR in breast and axilla (total pCR) after completion of study drug.

The tumor ORR will be calculated by treatment arm in all enrolled population and in *PIK3CA* MT population. Within each population, the ORR for the two treatment arms will be compared at a two-sided alpha of 16% using a Cochran Mantel-Haenszel test, stratified by tumor size and nodal status. The pCR rate will also be calculated and compared at a two-sided alpha of 4% based on the same analytical approach as ORR. The two alpha values account for a family-wise type I error rate of 20%. Patients with early study termination and hence missing efficacy outcome will be considered as non-responders.

### 6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are as follows:

- Tumor ORR after completion of study treatment, assessed by modified RECIST criteria by breast MRI *(centrally assessed)* in *PIK3CA* WT patients.

- Rate of pCR in breast and axilla (total pCR) after completion of study drug in *PIK3CA* WT patients.

  These endpoint measures will be summarized by treatment arm and will be analyzed analogue to the primary efficacy endpoint.

The following secondary efficacy endpoints will be performed in all enrolled patients and separated by *PIK3CA* mutation status *(centrally assessed)*:

- ORR *using modified RECIST criteria by the following methods:* clinical breast examination, mammography, and breast ultrasound
- Ki67 values at baseline, Week 3, and surgery (centrally assessed)
- Change in Ki67 from baseline to Week 3; baseline to surgery, and Week 3 to surgery (centrally assessed)
- PEPI score (centrally *derived*)
- Change in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluation of different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR)

These endpoint measures will be summarized by treatment arm and will be compared between the two treatment arms within each population based on appropriate statistical analyses: ORR will be compared using a Cochrane Mantel-Haenszel test, stratified by tumor size and nodal status; PEPI, Ki67, and tumor volume change will be compared by regression analyses, adjusted for tumor size and nodal status. All secondary endpoints will be tested at a two-sided type I error of 5%.

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

## 6.5 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, and letrozole and GDC-0032 exposure.

Verbatim descriptions of adverse events will be mapped to thesaurus terms. Adverse event data will be listed by study site, treatment arm, patient number, and study day, severity, relationship to study drug, outcome, and action taken with the study treatments. Events occurring on or after treatment on Day 1 of Week 1 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 and vital sign (heart rate, blood pressure, and temperature) data will be displayed by time, with NCI CTCAE v4.0 Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized in tables by NCI CTCAE v4.0 grade.

## 6.6 PHARMACODYNAMIC ANALYSES

Ki67 biomarker analyses will include patients with at least one predose and one postdose biomarker assessment, with patients grouped according to the treatment actually received.

## 6.7 PHARMACOKINETIC ANALYSES

Individual $C_{max}$ and trough plasma concentrations ($C_{min}$) of GDC-0032 and letrozole from all patients enrolled will be reported. Mean of trough plasma concentrations of GDC-0032 and letrozole will be tabulated. The population pharmacokinetics of letrozole and GDC-0032 in this study will be compared with historical single-agent pharmacokinetics to assess the potential DDI between GDC-0032 and letrozole in this population.

Additional PK analyses on metabolites of GDC-0032, letrozole, and/or other concomitant medications may be conducted as appropriate.

## 6.8 PATIENT-REPORTED OUTCOME ANALYSES

Patient-reported outcomes of breast cancer symptoms, patient functioning, and HRQoL will be assessed by the EORTC QLQ-C30 and the modified Breast Cancer module (QLQ-BR23)

Summary statistics (mean, standard deviation, median and range) of linear transformed scores will be reported for all the items and subscales of the EORTC QLQ-C30 questionnaire, and the modified QLQ-BR23 according to the EORTC scoring manual guidelines for each assessment time point. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) of items and subscales over time will be provided for each treatment arm from the baseline assessment.

Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results.

Completion and compliance rates will be summarized at each timepoint by treatment arm with reasons for missing data. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses. The number and proportion of patients who improved, worsened, or remained stable for all of the

symptom and functional domains, global QoL, and single items of the EORTC QLQ-C30 and QLQ-BR23 will be summarized.

## 6.9 EXPLORATORY ANALYSES

Additional details on analyses will be specified in the SAP.

## 6.10 INTERIM ANALYSES

The IDMC will conduct interim analyses to review the unblinded safety data after the first 20 patients have either 1) finished the 30-day, follow-up visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery)*, whichever occurs first*. All available information of all enrolled patients with all available assessments at the respective timepoint will be included in the interim analyses. In addition, the IDMC or the Medical Monitor may request additional ad hoc meetings of the IDMC at any time during the study to review safety data.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

ABCSG will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, ABCSG and/or all involved clinical research associates (CRAs) will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

ABCSG will produce a Data Management Plan that describes the quality checking to be performed on the data. The Sponsor will perform oversight of the data management of this study, including review of the ABCSG's data management plan and corresponding specifications. Data will be transferred electronically from ABCSG to the Sponsor at the end of the study and whenever otherwise contractually agreed, and the Sponsor's standard procedures will be used 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 at ABCSG and records retention for the study data will be consistent with the ABCSG's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff. Original PRO questionnaires will be kept in the patient's medical record as source documentation.

## 7.2 DATA(BASE) MANAGEMENT

ABCSG Clinical Data Management will check all e-forms for plausibility and consistency by automatic edit checks and manual data review according to study-specific data management plan (DMP). If necessary, web-based data queries (data clarification

requests [DCRs]) will be generated and subsequently visible for the investigators, dedicated site staff, responsible CRAs, and responsible ABCSG staff. For those eCRFs which pass all verification procedures and are regarded as correct and complete, they will be frozen subsequently by ABCSG clinical data management. Consequently, no further data entries or changes on frozen eCRFs are possible. The status of frozen eCRFs is flagged by the specific icon.

Clinical Data Management ensures that the database is corrected for the following eCRF issues without immediate notification to site staff (self-evident corrections). Notification of site staff is provided via a specific report after final data cleaning procedures and before final data confirmation by the investigator or a designee:

- misspellings/typing errors that do not change the meaning of the word
- location of data recorded at an incorrect variable field or eForm (e.g., moving lab data from general comments to the appropriate lab table)
- standard time to 24-hour clock
- correction of date format, if required (dd/mm/yyyy)
- if equivalent units of terms are recorded instead of the acceptable ABCSG standard
- data changes due to plausibility checks and eCRF content (e.g., combination of several variables and/or eCRFs)

All data management workflows are described in detail in the relevant SOPs and working instructions of ABCSG.

## 7.3 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using the Clinical Data Management System “MACRO,” a web-interface DATAPORT. Sites will receive training by the responsible CRAs and have access to a manual for appropriate eCRF completion (web data entry).

All eCRFs should be completed by designated, trained site staff in a timely manner, usually within 2 weeks after the patient visit. Electronic CRFs should be reviewed and respective data confirmation eCRF should be electronically signed and dated by the investigator or a designee at the end of the study.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a storage medium (compact disc [CD], digital video disk [DVD] etc.) that must be kept with the study records. Acknowledgement of receipt of the storage medium is required.

## 7.4 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

## 7.5 USE OF COMPUTERIZED SYSTEMS

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

## 7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data (if applicable), ICFs, 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 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP 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/European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

## 8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs) 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 ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved consent forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The ICF will contain a separate section that addresses the *consent for optional donation of remaining samples for the clinical repository. Samples stored in the clinical repository may be used for future exploratory research*. Patients will be told that they are free to refuse to *donate their remaining samples to the clinical repository. If patients choose to donate remaining samples, they* may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be *stored in the clinical repository.*

**The ICFs must be signed and dated by the patient or the patient's legally authorized representative before participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.** The eCRF contains a section to document whether the patient has signed the ICF or not.

The ICFs 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.

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs 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 ICF 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.

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the sponsor, the affiliated groups, or contract research organizations (CROs) according to the applicable local laws and regulations, if applicable 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 Sponsor, affiliated groups, or CROs are 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 local IRB/EC. The Sponsor, affiliated groups, or CROs 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 local health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 8.4 DATA PRIVACY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique 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 only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by local 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, provided the patient has given consent.

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. The patient will have to consent to such access by signing the informed consent form.

## 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (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, ICFs, and documentation of IRB/EC and governmental (health authorities) approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

## 9.2 ON SITE QUALITY CONTROL (MONITORING)

During the study, CRAs will visit their respective sites on a regular basis as outlined in the study specific monitoring plan (MP) and all other relevant specifications, in order to guarantee adherence to the protocol and to the principles of GCP and to check for the progress of enrolment, adequate storage conditions of IMP and adequate drug dispensing and accounting records.

CRAs will review documented data in the eCRFs for completeness and accuracy according to the study-specific MP, subsequently flag all reviewed pages with a specific mark ("SDV done") within the EDC system "MACRO," web-interface DATAPORT, developed by [redacted]. The CRAs will raise data queries ("DCRs") in cases of missing source data or incorrect data entries. Immediately after electronic issue of the queries, they become visible to the investigator, the clinical data managers, and the ABCSG clinical safety officers ("raised DCRs"). CRAs and/or clinical data managers and/or ABCSG clinical safety officers will follow up with trial site personnel until final data query resolution.

## 9.3 PROTOCOL DEVIATIONS

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

## 9.4 SITE INSPECTIONS

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

## 9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech and will be managed by Genentech in collaboration with the Breast International Group (BIG), ABCSG, and the *SOLTI* Breast Cancer Research Group. Genentech in collaboration with BIG, ABCSG, and SOLTI will

provide clinical operations management, data management, and medical monitoring. Approximately 110 U.S. and international sites will participate to enroll approximately 330 patients.

An IDMC will be in place throughout the study and will provide oversight of safety and efficacy analyses (see Section 3.1.2).

After written informed consent has been obtained, the study site will obtain the patient's screening number from the IxRS system. Once eligibility has been established, the patient will be enrolled, and the study site will obtain the patient's identification number from the IxRS. Once results of the tissue analysis are made available, the patient will be randomized, and the site will obtain the blinded treatment assignment from the IxRS. The IxRS will manage GDC-0032/placebo drug inventory at all sites and letrozole drug inventory at all study sites outside the United States. IxRS will be required to randomize patients, to monitor enrollment and patient status, and to manage study treatment requests and shipments.

Patient data will be recorded via an electronic data capture (EDC) system from [redacted] ([redacted], United Kingdom), which will be managed by ABCSG using eCRFs (see Section 7.2).

Central laboratories, including Genentech and Genentech collaborators, will be used for *PIK3CA* mutation detection, Ki67, and PTEN status and/or will provide kits for PK, pharmacogenomic, tissue, whole blood, and plasma sample analyses to be conducted at central laboratories, Genentech, or Genentech collaborators.

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

## 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

| Study procedures | Screening | Treatment Phase | | | | | | Surgery [a,f] | Post Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | W9 | W13 | W16 (Presurgical Visit) | W17 – W18 (Surgery) | 4 Weeks (+1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (±2) | 29 (±2) | 57 (±2) | 85 (±2) | 106 – 112 | 113 – 126 | |
| Informed consent [a] | x | | | | | | | | |
| Medical history and demographic data [b] | x | | | | | | | | |
| Physical examination [c] | x | | | x | x | x | x | | x |
| Clinical breast and regional lymph node examination | x | x | | x | x | x | x | | |
| Vital signs [d] | x | x | x | x | x | x | x | | x |
| ECOG Performance Status | x | x | x | x | x | x | x | | x |
| 12-Lead ECG [e] | x | | x | | | | | | |
| Mammography | x | | | | | | x | | |
| Breast ultrasound and axillary lymph node status [f] | x | | | | x | | x | | |
| Breast MRI [g] | x | | | | | | x | | |
| Collection of tumor samples [h] | x | | x | | | | | x | |
| Confirmation of receipt of adequate tissue for *PIK3CA* assessment | x | | | | | | | | |
| CBC with differential and platelet count [i] | x | x | | x | x | x | x | | x |
| Fasting serum chemistry [j] | x | x | | x | x | x | x | | x |

# Appendix 1
# Schedule of Assessments (cont.)

| Study procedures | Screening | Treatment Phase | | | | | | Surgery [a,f] | Post Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | W9 | W13 | W16 (Presurgical Visit) | W17 – W18 (Surgery) | 4 Weeks (+1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | 57 (±2) | 85 (±2) | 106 – 112 | 113 – 126 | |
| Glycosylated hemoglobin ($Hb_{A1c}$) | x | | | | | | | | |
| Fasting insulin and glucose [k] | x | x | | x | x | x | x | | x |
| Fasting lipid profile and amylase [l] | x | | | x | | x | x | | x |
| Coagulation (INR and aPTT) | x | | | x | x | x | x | | x |
| Urinalysis (laboratory) [m] | x | | | x | x | | x | | x |
| DLCO [n] | x | | | | | | x | | |
| Bone mineral density test [o] | x | | | | | | | | |
| Blood sample for plasma protein biomarkers [p] | | x | | | x | | x | | |
| Blood sample for ctDNA [q] | | x | | | x | | x | | |
| Blood sample for NGS [r] | | x | | | | | | | |
| Pharmacogenomic sample [s] | | x | | | | | | | |
| Concomitant medication [t] | x | x | x | x | x | x | x | | x |
| Adverse events | x | x | x | x | x | x | x | | x |
| Inclusion/exclusion criteria [u] | x | | | | | | | | |
| Visit with breast surgeon (may occur from Week 13) | | | | | | x | | | |
| Surgery [v] | | | | | | | | x | |
| Randomization | x | | | | | | | | |
| Letrozole accountability/dispensation | | x | x | x | x | x | x | | |

# Appendix 1
# Schedule of Assessments (cont.)

| Study procedures | Screening | Treatment Phase | | | | | | Surgery [a,f] | Post Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | W9 | W13 | W16 (Presurgical Visit) | W17 – W18 (Surgery) | 4 Weeks (+1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | 57 (±2) | 85 (±2) | 106 – 112 | 113 – 126 | |
| GDC-0032/placebo accountability/ dispensation | | x | x | x | x | x | x | | |
| Patient-reported outcomes [w] | | x | | x | x | x | x | | x |
| Pharmacokinetic sample (see Appendix 2) | | x | x | | x | | | | |

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; MRI = magnetic resonance imaging; NGS = next-generation sequencing.

Note: All assessments should be performed before dosing, unless otherwise stated. Some assessments may be performed outside the window indicated to accommodate holidays, unforeseen scheduling issues, or ongoing safety issues with the trial and the patient, after approval by the Medical Monitor.

[a] Perform within 28 days prior to Day 1 of Cycle 1. Signed informed consent must be provided prior to any study-specific evaluations. Assessments performed as standard of care within the timeframe may be used.

[b] Medical history includes clinically significant diseases that are currently active or that were active within the last 5 years, surgeries, cancer history (including date of diagnosis, primary tumor histology, grade, staging, prior cancer therapies, and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse. Demographic data include age, sex, and self-reported race/ethnicity.

[c] A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems as well as weight (in kilograms) and height (in centimeters; height is measured at the screening visit only). Perform symptom-directed physical examination after baseline assessment.

[d] Vital signs include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position and temperature. Oxygen saturation is obtained by pulse oximetry after the patient has been in a seated position for ≥ 5 minutes. Obtain vital signs predose.

[e] Triplicate ECG recordings will be obtained at each specified timepoint. A window of ± 30 minutes is acceptable for all timepoints. Submit all ECGs to the diagnostic facility for central review.

[f] Baseline evaluation of axillary lymph nodes assessed with ultrasound.

[g] MRI evaluation is optional at Week 9. MRI is mandatory at Week 9 in the event that disease progression is suspected, or if the primary lesion is not evaluable by ultrasound at baseline. Send all scans to the central reading facility for evaluation.

# Appendix 1
# Schedule of Assessments (cont.)

[h] Two formalin-fixed, paraffin-embedded core needle biopsies and one freshly frozen OCT core needle biopsy are required prior to initiation of treatment (pretreatment) and also on Day 15. A formalin-fixed, paraffin-embedded tumor block from a surgical resection is required at surgery (Weeks 17 – 18).

[i] Complete blood count includes red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[j] Fasting ($\geq$10-hour fast) serum chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[k] Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[l] Fasting lipid profile includes total cholesterol, HDL, LDL, triglycerides, amylase, and lipase. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[m] Includes specific gravity, pH, glucose, protein, ketones, and blood. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[n] DLCO is obtained at screening and prior to surgery. The DLCO test should be repeated if there is clinical suspicion of pneumonitis. DLCO calculations are described in Appendix 7. The hemoglobin value used for correcting DLCO should represent the patient's actual hemoglobin level and should be obtained within 7 days of the DLCO test.

[o] Baseline bone mineral density will be measured via dual-energy X-ray absorptiometry (DXA) and will need to be obtained in women with a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis. DXA measurement of both the hip and lumbar spine is suggested. When either the hip or lumbar spine is not a valid skeletal site for BMD measurement, then the 33% (one-third) radius should be measured. In some patients, measurement of the hip alone could be sufficient.

[p] Pretreatment sample for plasma protein biomarkers should be obtained prior to dosing. Refer to laboratory manual for more information.

[q] Pretreatment sample for ctDNA may be obtained on Day 1 prior to dosing. This sample will also be collected prior to dosing at Week 9 and at Week 16. Refer to laboratory manual for more information.

[r] Blood for NGS will be collected if allowed by local regulatory authorities and may be obtained prior to dosing on Week 1.

[s] Blood for pharmacogenomics will be collected if allowed by local regulatory authorities and may be obtained prior to dosing on Week 1.

[t] Record all medications used by the patient within 7 days before screening (including prescription, over-the-counter, herbal remedies, and supplements).

[u] All of the study's inclusion criteria and none of the exclusion criteria should be met prior to study entry.

[v] Surgery will take place after at least 16 weeks of combination treatment (i.e., from Week 17 to Week 18), and generally no more than 4 days after the last dose of study medication.

[w] The PRO questionnaires (EORTC QLQ-C30, modified QLQ-BR23) will be completed by the patients at the investigational site. All PRO questionnaires must be administered prior to any other study assessment(s) and prior to administration of study drug.

# Appendix 2
# Schedule of Pharmacokinetic Assessments

| Visit | Timepoint | PK Assessments |
|---|---|---|
| Day 1 | 3 hours post (±60 min) letrozole and GDC-0032/placebo administration | Letrozole PK |
| | | GDC-0032 PK |
| Day 15 (+2 days) | 0 – 4 hours prior to letrozole and GDC-0032/placebo administration | Letrozole PK |
| | | GDC-0032 PK |
| | 3 hours (±60 min) post letrozole and GDC-0032/placebo administration<br>ECG before PK | Letrozole PK |
| | | GDC-0032 PK |
| Day 57 (+/– 2 days) | 3 hours post (±60 min) letrozole and GDC-0032/placebo administration | Letrozole PK<br>GDC-0032 PK |

ECG = electrocardiogram; min = minutes; PK = pharmacokinetics.

Record exact time of dose administration and sample collection.

# 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 |

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 therapy in early breast cancer. Ultrasound, mammography, and clinical exam are all

[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.

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

### 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

## 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.

**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.

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

## 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
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures

## EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): _____

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

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

Please go on to the next page

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

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

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

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

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

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 31. Did you have a dry mouth? | 1 | 2 | 3 | 4 |
| 32. Did food and drink taste different than usual? | 1 | 2 | 3 | 4 |
| 33. Were your eyes painful, irritated or watery? | 1 | 2 | 3 | 4 |
| 34. Have you lost any hair? | 1 | 2 | 3 | 4 |
| 35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair? | 1 | 2 | 3 | 4 |
| 36. Did you feel ill or unwell? | 1 | 2 | 3 | 4 |
| 37. Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 38. Did you have headaches? | 1 | 2 | 3 | 4 |
| 39. Have you felt physically less attractive as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 40. Have you been feeling less feminine as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 41. Did you find it difficult to look at yourself naked? | 1 | 2 | 3 | 4 |
| 42. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 43. Were you worried about your health in the future? | 1 | 2 | 3 | 4 |
| 44. Have you had skin problems (e.g. itchy, dry)? | 1 | 2 | 3 | 4 |
| 45. Did itching of your skin bother you? | 1 | 2 | 3 | 4 |
| 46. Have you had a sore mouth or tongue? | 1 | 2 | 3 | 4 |
| 47. Have you had trouble swallowing? | 1 | 2 | 3 | 4 |

Please go on to the next page

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

| **During the past four weeks:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 48. To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 49. To what extent were you sexually active? (with or without intercourse) | 1 | 2 | 3 | 4 |
| 50. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |

# Appendix 5
# New York Heart Association Classifications

## Clinical Evaluation of Functional Capacity of Patients

| NYHA | Functional Class | Description | Objective Assessment |
|---|---|---|---|
| I | Mild | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea. | No objective evidence of cardiovascular disease. |
| II | Mild | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea | Objective evidence of minimal cardiovascular disease |
| III | Moderate | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea. | Objective evidence of moderately severe cardiovascular disease. |
| IV | Severe | Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. | Objective evidence of severe cardiovascular disease. |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors

## Tumor (T)

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ |
| Tis (DCIS) | DCIS |
| Tis (LCIS) | LCIS |
| Tis (Paget) | Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted. |
| T1 | Tumor ≤20 mm in greatest dimension |
| T1mi | Tumor ≤1 mm in greatest dimension |
| T1a | Tumor >1 mm but ≤5 mm in greatest dimension |
| T1b | Tumor >5 mm but ≤10 mm in greatest dimension |
| T1c | Tumor >10 mm but ≤20 mm in greatest dimension |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors (cont.)

## Tumor (T)

| | |
|---|---|
| T2 | Tumor >20 mm but ≤50 mm in greatest dimension |
| T3 | Tumor >50 mm in greatest dimension |
| T4 | Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)[a] |
| T4a | Extension to the chest wall, not including only pectoralis muscle adherence/invasion |
| T4b | Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma |
| T4c | Both T4a and T4b |
| T4d | Inflammatory carcinoma |

Reprinted with permission from AJCC: Breast. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 347–76.

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

Note: The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cut-off for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cut-off. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

[a] Invasion of the dermis alone does not qualify as T4.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors (cont.)

## Regional Lymph Nodes (N)

| Clinical | |
|---|---|
| NX | Regional lymph nodes cannot be assessed (e.g., previously removed) |
| N0 | No regional lymph node metastases |
| N1 | Metastases to movable ipsilateral level I, II axillary lymph node(s) |
| N2 | Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted |
| | OR |
| | Metastases in clinically detected [a] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases |
| N2a | Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures |
| N2b | Metastases only in clinically detected [a] ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases |
| N3 | Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement |
| | OR |
| | Metastases in clinically detected [a] ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases |
| | OR |
| | Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement |
| N3a | Metastases in ipsilateral infraclavicular lymph node(s) |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Regional Lymph Nodes (N)

| | Clinical |
|---|---|
| N3b | Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s) |
| N3c | Metastases in ipsilateral supraclavicular lymph node(s) |

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[a] Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pNX | Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study) |
| pN0 | No regional lymph node metastasis identified histologically |
| Note: ITCs are defined as small clusters of cells ≤0.2 mm, or single tumor cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by IHC methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated. | |
| pN0(i–) | No regional lymph node metastases histologically, negative IHC |
| pN0(i+) | Malignant cells in regional lymph node(s) ≤0.2 mm (detected by H&E or IHC including ITC) |
| pN0(mol–) | No regional lymph node metastases histologically, negative molecular findings (RT-PCR) |
| pN0(mol+) | Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC |
| pN1 | Micrometastases |
| | OR |
| | Metastases in 1–3 axillary lymph nodes |
| | AND/OR |
| | Metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| pN1mi | Micrometastases (>0.2 mm and/or >200 cells but none >2 mm) |
| pN1a | Metastases in 1–3 axillary lymph nodes, at least one metastasis >2 mm |
| pN1b | Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pN1c | Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected |
| pN2 | Metastases in 4–9 axillary lymph nodes |
| | OR |
| | Metastases in clinically detected [a] internal mammary lymph nodes in the absence of axillary lymph node metastases |
| pN2a | Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit $>2$ mm) |
| pN2b | Metastases in clinically detected[d] internal mammary lymph nodes in the absence of axillary lymph node metastases |
| pN3 | Metastases in $\geq 10$ axillary lymph nodes |
| | OR |
| | Metastases in infraclavicular (level III axillary) lymph nodes |
| | OR |
| | Metastases in clinically detected[c] ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes |
| | OR |
| | Metastases in $>3$ axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| | OR |
| | Metastases in ipsilateral supraclavicular lymph nodes |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pN3a | Metastases in ≥ 10 axillary lymph nodes (at least 1 tumor deposit >2 mm) |
| | OR |
| | Metastases to the infraclavicular (level III axillary lymph) nodes. |
| pN3b | Metastases in clinically detected [b] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; |
| | OR |
| | Metastases in > 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| pN3c | Metastases in ipsilateral supraclavicular lymph nodes |
| **Post-treatment ypN** | |
| Post-treatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "SN" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by AND. | |
| The X classification will be used (ypNX) if no yp post-treatment SN or AND was performed | |
| N categories are the same as those used for pN | |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

AND = axillary node dissection; H&E = hematoxylin and eosin stain; IHC = immunohistochemical; ITC = isolated tumor cells; RT-PCR = reverse transcriptase/polymerase chain reaction.

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[1] Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (SN) for "sentinel node," for example, pN0(SN).

[a] "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

[b] "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine-needle aspiration biopsy with cytologic examination.

## Distant Metastases (M)

| | |
|---|---|
| M0 | No clinical or radiographic evidence of distant metastases |
| cM0(i+) | No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other non-regional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases |
| M1 | Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm |

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**Post-treatment yp M classification.** The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pre-therapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Anatomic Stage/Prognostic Groups[a]

| Stage | T | N | M[c] |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| IA | T1[c] | N0 | M0 |
| IB | T0 | N1mi | M0 |
| | T1[c] | N1mi | M0 |
| IIA | T0 | N1[b] | M0 |
| | T1[c] | N1[b] | M0 |
| | T2 | N0 | M0 |
| IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| IIIA | T0 | N2 | M0 |
| | T1[c] | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| IIIB | T4 | N0 | M0 |
| | T4 | N1 | M0 |

## Appendix 6
## American Joint Committee on Cancer TNM Classification of Malignant (cont.)

| Stage | T | N | Mc |
|---|---|---|---|
| | T4 | N2 | M0 |
| IIIC | Any T | N3 | M0 |
| IV | Any T | Any N | M1 |

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Note: Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy. Post-neoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0cM0.

[a] T1 includes T1mi.

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

[c] M0 includes M0(i+); The designation pM0 is not valid; any M0 should be clinical. If a patient presents with M1 prior to NAST, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.

# Appendix 7
# Correction of Predicted DLCO for Hemoglobin and Alveolar Volume

All DLCO measurements will be obtained as per the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines (MacIntyre et al. 2005).
The predicted DLCO value should be corrected for both hemoglobin ($H_b$) and alveolar volume ($v_a$).

Pulmonary function test laboratories that follow the ATS/ERS guidelines should be able to provide the value for DLCO, corrected for $v_a$. A single breath $v_a$ may be used to obtain DLCO, corrected for va. Use the following equation to determine the predicted DLCO, corrected for $H_b$ and $v_a$:

> Predicted DLCO, corrected for $H_b$ and $v_a$ = [DLCO, corrected for $v_a$] $\times$ [1.7 $\times$ $H_b$ / (9.38 + $H_b$)]

Use the formula below to determine the percentage of predicted DLCO value (now corrected both for $H_b$ and $v_a$):

> **% of predicted DLCO** (corrected for $H_b$ and $v_a$) = [actual DLCO / (predicted DLCO corrected for $H_b$ and $v_a$)] $\times$ 100

# PROTOCOL

| | |
|---|---|
| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2-NEGATIVE, EARLY STAGE BREAST CANCER** |
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38/ NCT02273973 |
| **VERSION NUMBER:** | 2 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | 110184 |
| **TEST PRODUCT:** | GDC-0032 |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.D. |
| **SPONSOR:** | Genentech, Inc. |
| **DATE FINAL:** | Version 1: 23 December 2013 |
| **DATE AMENDED:** | Version 2: See electronic date stamp below |

## PROTOCOL AMENDMENT APPROVAL

| Approver's Name | Title | Date and Time (UTC) |
|---|---|---|
| [redacted] | [redacted] | 09-Apr-2014 17:34:39 |

## PROTOCOL AMENDMENT, VERSION 2:
## RATIONALE

Protocol GO28888 has been amended to include the following major changes:

- Language has been amended to clarify that the investigator has the sole responsibility to break the treatment code in emergency situations. These changes have been incorporated into Section 4.2.3 of the study protocol.
- Because pneumonitis is a known GDC-0032 toxicity, additional screening and management of pulmonary function is an important safety consideration for this trial. Exclusion criteria have been updated to exclude patients with diffusion capacity of the lung for carbon monoxide (DLCO) values $<$ 60% of predicted (Section 4.1.2). Calculations for DLCO have been included in Appendix 7. Management guidelines for pneumonitis (Section 5.1.1.2) have been updated to repeat the DLCO test if there is clinical suspicion of pneumonitis. The schedule of assessments has been updated to include DLCO testing at baseline and at the end of study treatment (Appendix 1, footnote n). Additional language describing DLCO testing has been added to the study assessments in Section 4.5.11.13.
- To ensure that the appropriate patients are enrolled into this study, exclusion criteria have been updated (Section 4.1.2) as follows:
  - Patients for whom upfront chemotherapy is clinically judged appropriate as optimal neoadjuvant treatment will be excluded from this study.
  - Patients for whom immediate surgery is indicated will be excluded from this study.
- Because letrozole is a potent estrogen-lowering agent, it can cause bone loss and may increase the risk of fractures. Section 4.5.11.14 has been amended to include a baseline bone mineral density assessment and adequate monitoring of women with a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis. The schedule of assessments (Appendix 1, footnote o) has been updated to reflect these changes. In addition, protocol language has been added to ensure appropriate monitoring.
- Section 4.4.2 has been amended to clarify that bisphosphonates can be used for the treatment of osteoporosis.
- The list of prohibited therapies in Section 4.4.2 has been updated to include potent CYP3A4 inducers.

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 2: SUMMARY OF CHANGES

### PROTOCOL AMENDMENT ACCEPTANCE FORM

A Protocol Amendment Acceptance Form has been added.

### LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The list of abbreviations has been updated to reflect changes to the protocol.

### PROTOCOL SYNOPSIS

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

### SECTION 4.1.2: Exclusion Criteria

- *Patients for whom upfront chemotherapy is clinically judged appropriate as optimal neoadjuvant treatment*
- *Patients for whom immediate surgery is indicated*
- *DLCO < 60% of the predicted values (see Appendix 7 for calculations)*

### SECTION 4.2.3: Blinding

~~If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment),~~ *For emergency situations,* the investigator will be able to break the treatment code by contacting the IxRS ~~following approval from~~. *The responsibility to break the treatment code in emergency situations resides solely with* the ~~Medical Monitor. Treatment codes should not be broken except in emergency situations where unblinding is needed for treatment decisions. Effort should be made~~ *investigator. For non-emergency situations, the investigator needs to obtain approval from* the Medical Monitor ~~before unblinding. Patient treatment assignment may be unblinded at the~~ *to break* the ~~patient discontinues from the blinded treatment phase at the request of the treating physician by contacting the IxRS following approval from the Medical Monitor and stating the reason for unblinding.~~ *treatment code.*

### SECTION 4.4.2: Prohibited Therapy

- **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. Patients who develop osteopenia or osteoporosis in the follow up period may receive bone targeted therapy as per the clinician's discretion. Primary use of bisphosphonates as a prevention of bone metastasis or as a prevention of bone loss is prohibited~~. …

- ***Potent CYP3A4 inducers:*** *Concomitant use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, phenobarbital) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to induce CYP3A4. If a strong CYP3A4 inducer is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.*

### SECTION 4.5.11.13: *DLCO Testing*

*A diffusion capacity of the lung for carbon monoxide (DLCO) test will be required at baseline and at the end of study-drug treatment (prior to surgery) for all patients. The DLCO test should be repeated if there is clinical suspicion of pneumonitis. Further guidance regarding DLCO testing is contained in Appendix 7 and in the management guidelines for pneumonitis (Section 5.1.1.2).*

### SECTION 4.5.11.14: *Osteoporosis Assessment and Monitoring*

*Treatment with aromatase inhibitors results in bone loss due to estrogen deficiency. For patients who have a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis, a bone mineral density assessment will be required at baseline prior to initiating study treatment. Baseline bone mineral density will be measured via dual-energy X-ray absorptiometry (DXA). DXA measurement of both the hip and lumbar spine is suggested. When either the hip or lumbar spine is not a valid skeletal site for a bone mineral density measurement, then the 33% (one-third) radius should be measured. In some patients, measurement of the hip alone could be sufficient.*

*Appropriate monitoring in these patients will occur per institutional guidelines. Assessment for fractures is already included as part of the scheduled physical examinations. Determination of patients who are at increased risk for osteoporosis will be per institutional guidelines. Clinical risk factors for fracture include advancing age, previous fracture, glucocorticoid therapy, parental history of hip fracture, low body weight, current cigarette smoking, excessive alcohol consumption, rheumatoid arthritis, and secondary osteoporosis (e.g., hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease) (Kanis et al., 2005).*

### SECTION 5.1.1.2: Management of Pneumonitis

*Patients who have DLCO values <60% will be excluded from the study. … The DLCO test should be repeated if there is clinical suspicion of pneumonitis. The DLCO test will also be repeated presurgery after completion of study treatment.*

### TABLE 3: Dose Modification and Management Guidelines for Pneumonitis

Table 3 has been revised to include diffusion capacity of the lung for carbon monoxide (DLCO) testing for managing pneumonitis.

## REFERENCES:

The following references have been added:

*Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteopors Int 2005;16:581– 9.*

*MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Resp J 2005;26:720–35.*

## APPENDIX 1: Schedule of Assessments

The schedule of assessments has been revised to reflect the changes to the protocol.

## APPENDIX 7: *Correction of Predicted DLCO for Hemoglobin and Alveolar Volume*

Appendix 7 has been added to provide DLCO calculations.

## SAMPLE INFORMED CONSENT FORMS

The sample Informed Consent Forms have been revised to reflect the changes to the protocol.

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## PROTOCOL AMENDMENT ACCEPTANCE FORM

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|---|---|
| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2-NEGATIVE, EARLY STAGE BREAST CANCER** |
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38 |
| **VERSION NUMBER:** | 2 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | 110184 |
| **TEST PRODUCT:** | GDC-0032 |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.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 return the signed original of this form as instructed by your local study monitor. Please retain a copy for your study files.

**Principal Investigators:**

[redacted]

| Author(s): | Affiliation |
|---|---|
| [redacted] | [redacted], USA<br>[redacted], Belgium<br>[redacted], Diputació 256 4º1ª 08007 Barcelona, Spain<br>[redacted], Genentech, South San Francisco, CA, USA<br>[redacted], ABCSG, Nussdorfer Platz 8, 1190 Wien, Austria<br>[redacted], ABCSG, Nussdorfer Platz 8, 1190 Wien, Austria<br>[redacted], ABCSG, Austria<br>[redacted], Genentech, South San Francisco, CA, USA<br>[redacted], Genentech, South San Francisco, CA, USA<br>[redacted] Spain<br>[redacted] Spain<br>[redacted], Genentech, South San Francisco, USA<br>[redacted], Belgium<br>[redacted] Belgium<br>[redacted], Spain<br>[redacted], Diputació 256 4º1ª 08007 Barcelona, Spain<br>[redacted], Spain |

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2- NEGATIVE, EARLY STAGE BREAST CANCER** |
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38 |
| **VERSION NUMBER:** | 2 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | 110184 |
| **TEST PRODUCT:** | GDC-0032 |
| **PHASE:** | II |
| **INDICATION:** | Early stage breast cancer |
| **SPONSOR:** | Genentech, Inc. |

**Objectives**

**Efficacy Objectives**

The primary objective of this study is to evaluate the efficacy of letrozole plus GDC-0032 versus letrozole plus placebo in women with estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) early stage breast cancer, as measured by the following co-primary endpoints:

- Tumor overall objective response rate (ORR) by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in all enrolled patients and *PIK3CA* mutant (MT) patients
- Pathologic complete response (pCR) rate in breast and axilla (ypT0/Tis ypN0) by local evaluation in all enrolled patients and *PIK3CA* MT patients

The secondary efficacy objectives of this study are the following:

- Tumor objective response rate (ORR), assessed by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR ypT0/Tis ypN0) by local evaluation in *PIK3CA* wildtype (WT) patients

The following secondary objectives will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of locally assessed ORR using the following methods:
  - Breast ultrasound
  - Clinical breast exam (i.e., palpation)
  - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery.

- Compare the centrally assessed, preoperative endocrine prognostic index (PEPI) score upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo.
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment.
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

**Safety Objective**

The safety objective for this study is as follows:

- Evaluate the safety of letrozole plus GDC-0032 versus letrozole plus placebo

**Patient-Reported Outcome Objectives**

The patient-reported outcome (PRO) objectives for this study are as follows:

- Evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23)

**Exploratory Objectives**

The exploratory objectives for this study are as follows:

- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess whether biomarkers from tumor tissue or blood, including but not limited to somatic cancer associated mutations, PTEN expression, pro-survival pathways (such as PI3K/AKT, MAPK etc.), apoptotic markers, and levels of RNA and DNA expression are predictive of response
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to anti-tumor activity
- To assess concordance and percentage of *PIK3CA* mutation status from baseline biopsy and surgical specimen
- To assess emergence of resistance alleles from tumor tissue or blood
- To assess concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response
- To assess the pharmacokinetics and possible drug interaction between letrozole and GDC-0032 upon concomitant administration
- To assess the correlation of GDC-0032 drug levels and GDC-0032 related response (efficacy or adverse events [e.g., colitis, rash])
- To assess the influence of pharmacogenetic polymorphisms on GDC-0032 and/or letrozole on pharmacokinetics and response (either efficacy and/or adverse events)
- Compare the rates of breast-conserving surgery (BCS) and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo.

## Study Design

**Description of Study**

This is a two-arm, randomized, double-blind, multicenter, pre-operative study to evaluate the effect of combining letrozole and GDC-0032 versus letrozole and placebo in postmenopausal women with ER+/HER2- untreated, Stage I-III operable breast cancer whose primary tumors are $\geq$ 2 cm. Patients with cT4 or cN3 tumors are not eligible. Standard of care assessments/procedures (e.g., bilateral mammogram) performed within 28 days of Day 1 dosing do not need to be repeated for screening purposes.

All patients will undergo pretreatment tumor tissue acquisition (snap-frozen [optimal cutting temperature; OCT] and formalin-fixed paraffin-embedded cores [FFPE]). Two pretreatment FFPE core biopsies and one freshly frozen core biopsy must be obtained for all patients prior to beginning study drug treatment. Prior diagnostic FFPE core biopsies may be used for enrollment eligibility purposes. For the purpose of enrollment, ER, progesterone receptor (PR), and HER2 will be locally determined prior to beginning of study treatment. ER, PR, HER2, and

the percentage of Ki67-positive cells will also be centrally assessed, but the results do not have to be available prior to enrollment in the study. Remaining tissue will be retained for future translational studies. Pre-surgical sentinel lymph node biopsy (SLNB) is not allowed.

Patients will be randomized into one of the two treatment arms with a 1:1 randomization ratio. Letrozole at 2.5 mg will be dosed once daily plus either GDC-0032 at 6 mg or placebo on a 5 – days-on/ 2 – days-off schedule for a total of 16 weeks (see Figure 5). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

After confirmation of all the eligibility criteria, patients will be randomized to one of the treatment arms. A second biopsy will be performed on Day 15 (Week 3) for biomarker analyses. Biopsies should be performed at least 2 hours after GDC-0032 dose administration.

Randomization will be stratified according to 2 factors:

1. Tumor size (T1-T2 vs. T3)
2. Nodal status (cytologically positive vs. radiologically or cytologically negative)

The study will enroll approximately 330 patients at approximately 110 global sites.

At Weeks 1, 5, 9, 13, and 16 the primary breast tumor and axillary lymph nodes will be assessed by clinical breast examination (palpation and caliper measurement). Suspicion of progression based on clinical exam at any time should be further evaluated (Figure 6).

At Week 9, a breast ultrasound will be performed to ensure that there is no progressive disease and for the purpose of surgery planning. Suspicion of progressive disease on breast ultrasound should be confirmed by investigator-assessed breast MRI. Patients with primary disease not evaluable by ultrasound at baseline should be assessed by MRI at Week 9. Suspected progression in nodes should also be confirmed by fine needle aspiration (FNA) if these nodes had not been previously shown to be cytologically positive for cancer. Patients with progressive disease (as defined by modified RECIST, Appendix 3), can either proceed directly to surgery or be taken off of the study, according to the investigator's decision. If the patient goes off-study, every reasonable effort should be made to obtain a new biopsy prior to beginning another systemic treatment.

From Week 13, the patient will visit with the surgeon. The purpose of this visit is two-fold: tentative planning of the type of breast surgery to be performed (breast conservative vs. mastectomy) and scheduling the date for definitive surgery.

During Week 16, breast MRI will be done for the purpose of primary endpoint analysis. Clinical breast exam, breast ultrasound, and mammography will also be conducted prior to surgery for the purpose of the secondary endpoint analysis.

Blood sample for exploratory endpoint analysis will be collected at screening, at Week 3, and prior to surgery.

**Surgery**

Surgery will take place after at least 16 weeks of treatment, during Weeks 17 – 18. Surgery should be performed within 4 days after the last dose of GDC-0032, if possible, to best observe pharmacodynamic knockdown with GDC-0032 in the surgical specimen. Surgery may be delayed due to toxicity or other safety issues, upon discussion with the Medical Monitor (see Section 5.4.1) or recommendations from the Independent Data Monitoring Committee (IDMC; see below). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

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. Surgery specimens will be collected for histological examination to assess for pCR and for other endpoint analyses.

Following surgery, follow-up will proceed according to local standards of care. Adjuvant endocrine therapy and/or chemotherapy will be delivered as per the investigator's choice. Postoperative radiotherapy is required if BCS is performed. In the event of mastectomy, radiotherapy is to be administered according to local guidelines.

A postsurgery visit will be performed 4 weeks (+ 1 week) after surgery, and will mark the end of the study. Assessment of adverse events and general safety will be collected at this visit and the plan for future treatment will be recorded.

The patient should be evaluated at baseline and after Week 13 of treatment for planning of the surgical procedure (BCS or mastectomy), and both physician recommendation and final patient decision should be documented in the electronic Case Report Form (eCRF).

The co-primary efficacy endpoint, pathological complete response (pCR–ypT0/is, ypN0) will be established via a local review following completion of neoadjuvant therapy and surgery.

Please refer to the pathology manual for further guidance of evaluation for pCR and directions for sending a copy of the pathology report.

A schedule of assessments is provided in Appendix 1.

An Independent Review Facility (IRF) will be used to determine the tumor ORR via MRI. IRF procedures are detailed in the IRF charter.

**Number of Patients**

The study will enroll approximately 330 patients at approximately 110 global sites.

**Target Population**

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF) prior to any study-specific procedure
- Female patients
- Postmenopausal status and age ≥ 18 years. Postmenopausal status is defined as follows:
  - Age ≥ 60 years or
  - Age < 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment or
  - Prior bilateral oophorectomy (≥ 28 days prior to Day 1 of treatment)
- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor ≥ 2 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 ≥ 2 cm and designated as the "target" lesion for all subsequent tumor evaluations.
  - Stage I to operable Stage III breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms).
- ER-positive and HER2-negative breast cancer, as per local laboratory or regional definition
- Breast cancer eligible for primary surgery
- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for *PIK3CA* mutation status by central histopathology laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Fasting glucose ≤ 125 mg/dL
- Adequate hematological, renal, and hepatic function, as follows:
  - Absolute neutrophil count ≥ 1500/μL
  - Platelets count ≥100,000/μL
  - Hemoglobin ≥ 9 g/dL
  - Serum bilirubin ≤ 1.5 × the upper limit of normal (ULN)
  - Patients with known Gilbert's disease who have serum bilirubin ≤ 3 × ULN may be enrolled
- Aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase ≤ 1.5 × ULN

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation:

  $(140 - \text{age}) \times (\text{weight in kg}) \times (0.85)$
  $72 \times (\text{serum creatinine in mg/dL})$
- International normalized ratio (INR) $< 1.5 \times$ ULN and activated partial thromboplastin time (aPTT) $< 1.5 \times$ ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2–3 is required. If anticoagulation is required for a prosthetic heart valve, then INR should be between 2.5–3.5.
- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Ability and willingness to comply with study visits, treatment, testing, and to comply with the protocol, in the investigator's judgment

Exclusion Criteria

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

- Any prior treatment for primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer
- 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 sentinel lymph node biopsy prior to study treatment
- *Patients for whom upfront chemotherapy is clinically judged appropriate as optimal neoadjuvant treatment*
- *Patients for whom immediate surgery is indicated*
- Type 1 or 2 diabetes requiring antihyperglycemic medication
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteric absorption
- History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis)
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF) $>$ 470 msec
- *DLCO < 60% of the predicted values (see Appendix 7 for calculations)*
- Clinically significant (i.e., active) cardiovascular disease, like uncontrolled hypertension, unstable angina, history of myocardial infarction, cardiac failure class II-IV (New York Heart Association, Appendix 5), or any other that in the judgment of the investigator could jeopardize patient safety or study outcomes
- 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
- Active infection requiring intravenous (IV) antibiotics
- Patients requiring any daily supplemental oxygen
- Clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis
- Known human immunodeficiency virus (HIV) infection
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications
- Significant traumatic injury within 3 weeks prior to initiation of study treatment
- Major surgical procedure within 4 weeks prior to initiation of study treatment
- Inability to comply with study and follow-up procedures
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

**Concomitant 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 7 days prior to screening to the study completion/discontinuation visit.

GDC-0032 was metabolized primarily by CYP3A4 in HLM and appeared to be a weak time dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low-to-moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC 0032 may be administered concomitantly with CYP3A4 substrates without the risk of a pharmacokinetic drug-drug interaction (DDI).

**Prohibited Therapy**

Prohibited therapy is as follows:

- **Anti-cancer therapy:** No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than letrozole permitted in this protocol) will be allowed.
- **Hormone replacement therapy**, **topical estrogens (including any intra-vaginal preparations), hormonal contraception, megestrol acetate, and selective estrogen-receptor modulators used with prophylactic intent**: If a patient is receiving these at the moment of registration, treatment should be discontinued prior to randomization.
- **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.
- **Potent CYP3A4 inhibitors:** Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole and itraconazole) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If a strong CYP3A4 inhibitor is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.

- ***Potent CYP3A4 inducers:*** *Concomitant use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, phenobarbital) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to induce CYP3A4. If a strong CYP3A4 inducer is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.*

**Length of Study**

The total duration of the study is expected to be approximately 24 months for enrollment, plus 5.5 months after last patient in.

**End of Study**

The end of the study is defined as the date when the last patient has her postsurgery visit.

**Outcome Measures**

**Co-Primary Efficacy Outcome Measures**

The co-primary efficacy outcome measures for this study are as follows:

- Tumor ORR via centrally assessed breast MRI via modified RECIST (Appendix 3) in all enrolled patients and *PIK3CA* MT patients
- pCR rate in breast and axilla (total pCR) as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system (Appendix 6) by local evaluation in all enrolled patients and *PIK3CA* MT patients

**Secondary Efficacy Outcome Measures**

The secondary efficacy outcome measures for this study are as follows:

- Tumor ORR, assessed by centrally assessed breast MRI via modified RECIST (Appendix 3) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR) by local evaluation in *PIK3CA* WT patients

The following secondary outcome measures will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of ORR, as measured by modified RECIST criteria (Appendix 3) using the following methods:
  - Breast ultrasound
  - Clinical breast exam (i.e., palpation)
  - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally assessed PEPI score upon treatment with letrozole plus GDC-0032 with letrozole plus placebo
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) yoT0/is, ypNX (breast pCR)

**Safety Outcome Measures**

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0)
- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Serious adverse events
- Protocol-defined adverse events of special interest
- Clinically significant changes in vital signs and in clinical laboratory results during the adverse event reporting period (see Section 5.3.1)

**Patient-Reported Outcome Measures**

The PRO outcome measures for this study are as follows:

- HRQoL, including side-effects of therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems), and patient functioning as measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ–C30) and the modified breast cancer module QLQ–BR23

**Exploratory Outcome Measures**

The exploratory outcome measures for this study are as follows:

- ORR, pCR rate, and PEPI scores according to the decrease in Ki67 after 2 weeks of letrozole plus GDC-0032 and letrozole plus placebo.
- Expression of biomarkers before, during, and after therapy. These include, but are not limited to, the following:
  - PI3K pathway aberrations
  - Gene signatures, including intrinsic subtyping and PI3K pathway activity
  - Protein and phospho-protein markers and combinations
  - Mutations within cancer-associated genes
  - Copy number alterations in cancer-related genes
  - Plasma-based protein biomarkers
  - Circulating tumor DNA (ctDNA)
- Compare the rates of BCS and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo
- The relationship between GDC-0032 concentration and tumor response and/or drug safety response
- Letrozole concentrations with and without administration of GDC-0032
- The relationship between pharmacogenetic differences in drug metabolizing enzymes and transporters and other patient-specific covariates with PK of GDC-0032 or letrozole and/or drug response
- Changes from baseline to surgery in the apparent diffusion coefficient (ADC), a marker of tumor cellularity derived from diffusion-weighted MRI
- Concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response

**Investigational Medicinal Products**

Study treatment is neoadjuvant (pre-operative) therapy.

**Test Product**

The test product for this study is GDC-0032. Patients will receive an oral, daily dose of 6 mg GDC-0032 or placebo on a schedule of 5 days on/2 days off for a maximum of 16 weeks. Patients will take GDC-0032 at the same time of day $\pm$2 hours, unless otherwise instructed. Patients will be instructed as to the number of tablets to take.

Information on the formulation, packaging, handling, and administration of GDC-0032 are provided in the GDC-0032 Investigator's Brochure.

**Non-Investigational Medicinal Products**

**Letrozole**

Letrozole is a marketed product that is approved in the European Union and the United States for the treatment of hormone receptor-positive breast cancer. Based upon the different mechanisms of action of GDC-0032 and the well-established safety profile of letrozole, there are no expected overlapping, significant toxicities between letrozole and GDC-0032.

Patients will receive an oral, daily dose of 2.5 mg letrozole for 16 weeks (or until time of surgery at the investigator's discretion).

## Statistical Methods

### Primary Analysis

This study is designed for testing the effect of GDC-0032 on the two co-primary endpoints in all enrolled patients and in the *PIK3CA* MT patients and plans to enroll 330 patients in total. Assuming the *PIK3CA* mutation status will not be available (unknown) for approximately 10% of the patients and the prevalence of *PIK3CA* mutant is 40%, there will be approximately 120 patients in the *PIK3CA* MT cohort.

Given that the *PIK3CA* mutation status is not a stratification factor for randomization, there might be a possible imbalance between treatment arms within the *PIK3CA* MT cohort, which may reduce the statistical power in this cohort. To ensure the study provides sufficient statistical power even when the treatment assignment is imbalanced, the sample size was calculated based on a conservative scenario by assuming that the treatment assignment imbalance in *PIK3CA* MT is 40% vs. 60%. The sample size was calculated based on a $chi^2$-test using continuity correction (Ury and Fleiss 1980).

To control an overall two-sided, family-wise error rate under 20%, we use a two-sided significance level of 16% and 4% for the co-primary endpoints MRI ORR, and pCR, respectively.

Assuming 10% of the patients are unevaluable for the MRI ORR, approximately 300 enrolled patients and 108 patients in the *PIK3CA* MT cohort will be evaluable for analyses. This sample size allows us to detect an absolute percentage increase of 24% in MRI ORR rate in the GDC-0032 plus letrozole arm (64%) versus the letrozole-only arm (40%; Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at 80% power and 16% two-sided significance level. The minimal detectable difference for ORR is approximately 15%.

Assuming that all patients are evaluable for pCR (i.e., approximately 330 enrolled patients and 120 in the *PIK3CA* MT cohort), this sample size provides 80% power to detect an absolute percentage increase of 18% in pCR in the GDC-0032 plus letrozole arm (19%) versus the letrozole-only arm (1%, Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at the 4% two-sided significance level. The minimal detectable difference for pCR rate is approximately 13%.

If the prevalence of the *PIK3CA* mutation is lower than assumed, if there is more substantial treatment assignment imbalance in the *PIK3CA* MT cohort than assumed, or there is an increased number of unevaluable patients for the MRI ORR, the sample size may be increased to obtain the level of power at 80%, and the enrollment may be limited to patients with *PIK3CA* MT.

### Secondary Analysis

The secondary efficacy endpoints for this study are as follows:

- Tumor ORR after completion of study treatment, assessed by modified RECIST criteria by breast MRI in *PIK3CA* WT patients.
- Rate of pCR in breast and axilla (total pCR) after completion of study drug in *PIK3CA* WT patients.

These endpoint measures will be summarized by treatment arm and will be analyzed analogue to the primary efficacy endpoint.

The following secondary efficacy endpoints will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- ORR by clinical breast examination, mammography and breast ultrasound
- Ki67 values at baseline, Week 3, and surgery (centrally assessed)
- Change in Ki67 from baseline to Week 3; baseline to surgery, and Week 3 to surgery (centrally assessed)
- PEPI score (centrally assessed)
- Change in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluation of different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

These endpoint measures will be summarized by treatment arm and will be compared between the two treatment arms within each population based on appropriate statistical analyses: ORR

will be compared using a Cochrane Mantel-Haenszel test, stratified by tumor size and nodal status; PEPI, Ki67, and tumor volume change will be compared by regression analyses, adjusted for tumor size and nodal status. All secondary endpoints will be tested at a two-sided type I error of 5%.

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

**Determination of Sample Size**

Please refer to the primary analysis in the Statistical Methods section.

**Interim Analyses**

An Independent Data Monitoring Committee (IDMC) will monitor accumulating patient safety data at a minimum of once every 6 months until the last patient has completed study treatment. Additional details (e.g., IDMC members, communication, affiliations) will be provided in the IDMC charter.

The IDMC will conduct interim analyses to review the unblinded safety data after the first 20 patients have either 1) finished the 30-day follow-up visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery). The IDMC will create and review unblinded, pooled summaries of the safety and available PK summaries (all interim analyses). While this review is being conducted, patient accrual into the study will continue. The Medical Monitor may also request additional safety analysis and may call for additional meetings of the IDMC to review ongoing safety data.

The IDMC will share results from interim safety analyses with the study team. The study team will share interim safety results with study investigators as needed for the conduct of the study and the safety of the patients. Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections. All available information of all enrolled patients with all available assessments at the respective timepoint will be included in the interim analyses.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ABCSG | Austrian Breast and Colorectal Cancer Study Group |
| ADC | apparent diffusion coefficient |
| AE | adverse events |
| AI | aromatase inhibitors |
| ALT | alanine transaminase |
| aPTT | activated partial thromboplastin time |
| ASCO-CAP | American Society of Clinical Oncology-College of American Pathologists |
| AST | aspartate aminotransferase |
| $AUC_{0-24}$ | area under the concentration–time curve from 0 to 24 hours |
| BCS | breast conserving surgery |
| BIG | Breast International Group |
| BUN | blood urea nitrogen |
| CD | compact disc |
| CI | confidence interval |
| $C_{max}$ | maximum plasma concentration observed |
| $C_{min}$ | minimum concentration under steady-state conditions within a dosing interval |
| cPR | confirmed partial responses |
| CRA | clinical research associate |
| CRO | contract research organization |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating tumor DNA |
| CTNeoBC | Collaborative Trials in Neoadjuvant Breast Cancer |
| DCR | data clarification request |
| DDI | drug-drug interaction |
| *DLCO* | *diffusion capacity of the lung for carbon monoxide* |
| DLT | dose-limiting toxicity |
| DMP | data management plan |
| *DXA* | *dual-energy X-ray absorptiometry* |
| DVD | digital video disk |
| EC | Ethics Committee |
| $EC_{50}$ | 50% effective concentration |
| ECG | electrocardiogram |

| Abbreviation | Definition |
|---|---|
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EGFR | epidermal growth factor receptor |
| ELISA | enzyme-linked immunosorbent assay |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ER+ | estrogen receptor-positive |
| E.U. | European Union |
| FFPE | formalin-fixed paraffin-embedded |
| FDA | Food and Drug Administration |
| FNA | fine needle aspiration |
| FSH | follicle stimulating hormone |
| GCP | good clinical practice |
| HbA1c | Glycosylated hemoglobin |
| HDL | high-density lipoprotein |
| HDPE | high-density polyethylene |
| HER2 | human epidermal growth factor receptor 2 |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HLA | human leukocyte antigen |
| HLM | human liver microsomes |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IHC | immunohistochemistry |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (application) |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IRF | Independent Review Facility |
| ISH | in situ hybridization |
| ITT | intent to treat |
| IV | intravenous |
| IxRS | interactive voice or web-based response system |

| Abbreviation | Definition |
|---|---|
| LDL | low-density lipoprotein |
| LPLV | last patient, last visit |
| MAPK | mitogen-activated protein kinase |
| MDD | minimum detected difference |
| MP | monitoring plan |
| MRI | magnetic resonance imaging |
| MT | mutant |
| MTD | maximum tolerated dose |
| mTOR | mammalian target of rapamycin |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NGS | next generation sequencing |
| NSCLC | non – small-cell lung cancer |
| nu/nu | immunocompromised nune (mice) |
| OCT | Optimal cutting temperature |
| ORR | objective response rate |
| pAKT | phosphorylated form of AKT |
| pCR | pathologic complete response |
| PD | progressive disease |
| PEPI | preoperative endocrine prognostic index |
| PFS | progression-free survival |
| PFT | pulmonary function test |
| PI3K | phosphatidylinositol-3-kinase |
| PIP2 | phosphatidylinositol-4,5-bisphosphate |
| PIP3 | phosphatidylinositol 3,4,5 trisphosphate |
| PO | oral |
| PR | progesterone receptor |
| PRO | patient-reported outcome |
| PTEN | phosphatase tensin homolog |
| QD | once daily |
| QLQ-BR23 | Quality of Life Questionnaire Breast Cancer Module |
| QLQ-C30 | Quality of Life Questionnaire Core 30 |
| QTcF | QT interval corrected using Fridericia's formula |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RFS | relapse-free survival |
| RPPA | reverse phase protein array |

| Abbreviation | Definition |
|---|---|
| RT-PCR | real-time polymerase chain reaction |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SDV | source data verification |
| SLNB | sentinel lymph node biopsy |
| SOLTI | Spanish Breast Cancer Research Group |
| SOP | standard operating procedure |
| SmPC | summary of product characteristics |
| $t_{1/2}$ | terminal half-life |
| TGI | tumor growth inhibition |
| ULN | upper limit of normal |
| U.S. | United States |
| WBC | white blood cell |
| WT | wildtype |

# 1. BACKGROUND

## 1.1 BACKGROUND ON THE PHOSPHATIDYLINOSITOL-3-KINASE PATHWAY

Phosphatidylinositol-3-kinase (PI3K) is a lipid kinase involved in tumor cell proliferation, survival, and migration upon activation by growth factor receptors and integrins. PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3) (Cantley 2002), a second messenger involved in the phosphorylation of AKT and associated proteins in the AKT-mammalian target of rapamycin (mTOR) pathway (Guertin and Sabatini 2007). Activating and transforming mutations, as well as amplification, in the p110$\alpha$ subunit of PI3K are commonly found in solid and hematological tumors (Li et al. 1997). In addition, the PI3K-AKT pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling, the loss of the phosphatase tensin homolog (PTEN), or RAS mutations (Shayesteh et al. 1999 ; Cantley 2002; Massion et al. 2004; Wu et al. 2005).

## 1.2 BACKGROUND ON ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER

Breast cancer is the most frequently diagnosed cancer worldwide and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of total cancer deaths (Jemal et al. 2011). As a large proportion of breast cancer cases, especially in developed countries, are now diagnosed in early stages, they are amenable to cure with a stage-appropriate combination of surgery, systemic therapy (chemotherapy and/or hormonal therapy), and radiotherapy.

Estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer accounts for about 60%–70% of all breast cancers. However, not all ER+ breast cancers respond optimally to endocrine therapy (Davies et al. 2011). There are several mechanisms that can lead to primary and/or secondary hormonal resistance in ER+ breast cancer: decrease of ER expression, loss of ER expression, or upregulation of growth factor signaling pathways, like the epidermal growth factor receptor (EGFR)/HER2, the mitogen-activated protein kinase (MAPK), or the PI3K/AKT/mTOR pathways (Johnston 2009).

In the setting of ER+/HER2-negative breast cancer, the PI3K/AKT/mTOR pathway plays an important role in mediating hormonal resistance and is a viable therapeutic target to explore (Miller et al. 2010).

## 1.3 BACKGROUND ON THE PI3K/AKT/MTOR PATHWAY AND BREAST CANCER

Genes in the PI3K/AKT/mTOR signaling pathway are frequently mutated or amplified in breast cancer, especially in the ER+ subtype (Cancer Genome Atlas Network 2012). Molecular alterations of the PI3K/AKT/mTOR pathway include the following: (1) Mutations or amplifications in *PIK3CA*, the gene encoding the alpha catalytic subunit of PI3K (p110$\alpha$) (Saal et al. 2005; Wu et al. 2005); (2) Alterations in the tumor suppressor gene PTEN, either by loss of protein expression (PTEN null), inactivation mutations and/or epigenetic deregulation through promoter hypermethylation (García et al. 2004); (3) PDKP1 amplification and/or overexpression (Brugge et al. 2007); (4) AKT1 somatic gain of function mutations (Stemke-Hale et al. 2008) and AKT2 amplifications (Bellacosa et al. 1995). Overall, it is estimated that up to 70% of breast cancers can have some form of molecular aberration of the PI3K/AKT/mTOR pathway (CGAN 2012).

## 1.4 BACKGROUND ON REVERSING HORMONAL RESISTANCE BY INHIBITING THE PI3K/MTOR/AKT PATHWAY

In the setting of ER+ breast cancer, PI3K seems to play an important role in mediating hormonal resistance and may be a viable therapeutic target. Hyperactivation of this signaling pathway was proved to promote both *de novo* and acquired resistance to hormone therapy in ER+ breast cancer cell lines and xenograft models (Sabnis et al. 2007), and simultaneous blocking of the PI3K/AKT/mTOR pathway with everolimus and the ER pathway with letrozole enhances antitumor activity of either agent alone (Boulay et al. 2005). Importantly, a baseline protein signature of PI3K activation was found to be predictive of a poor prognosis after adjuvant endocrine therapy (Miller et al. 2010).

In the clinical setting, impressive results of the combination of exemestane and everolimus, an mTOR inhibitor, were reported in the BOLERO-2 trial (Baselga et al. 2009). This trial compared everolimus and exemestane with placebo and exemestane in 724 postmenopausal patients with ER+ advanced breast cancer who had experienced recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting and/or in advanced disease. Median progression-free survival (PFS) in the everolimus group was 6.9 months, as compared to 2.8 months in the placebo group. Hazard ratio (HR) for progression or death was 0.43, with a 95% confidence interval (CI) of $0.35-0.54$ ($p<0.001$), as per the investigator's assessment, and the magnitude of the effect was even greater as per central assessment (HR, 0.36, 95% CI, $0.27-0.47$; $p<0.001$). In the open-label Phase II TAMRAD trial, patients with aromatase inhibitors (AI) resistant metastatic breast cancer received tamoxifen plus everolimus or tamoxifen alone (Bachelot et al. 2012). The 6-month clinical benefit rate was 61% (95% CI, $47\%-74\%$) with tamoxifen plus everolimus and 42% (95% CI, $29\%-56\%$) with tamoxifen alone. Time to progression increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus everolimus, corresponding to a 46% reduction in risk of progression with the combination

(HR, 0.54; 95% CI, 0.36 – 0.81). Risk of death was reduced by 55% with tamoxifen plus everolimus versus tamoxifen alone (HR, 0.45; 95% CI, 0.24 – 0.81).

In the neoadjuvant setting, combination of letrozole and everolimus also resulted in improved responses over letrozole alone in patients with ER+ breast cancer (Baselga et al. 2009). In this study, 270 postmenopausal patients with operable ER+ breast cancer were randomly assigned to receive 4 months of neoadjuvant treatment with letrozole and either everolimus or placebo. The primary endpoint of the trial, clinical response by palpation, was higher in the everolimus arm than in the control arm (68.1% vs. 59.1%, $p = 0.062$), a statistically significant result (one-sided, $\alpha = 0.1$ level).

An important finding in trials with mTOR-targeting drugs like everolimus is that they produce a pharmacodynamic paradox: while inhibiting mTOR, they lead to an upregulation of the phosphorylated form of AKT (pAKT), resulting in feedback PI3K/AKT/mTOR pathway activation (Tabernero et al. 2009). This finding suggests that alternative pharmacologic strategies to effectively shut down the pathway upstream of AKT should be pursued. One of these strategies is inhibiting the PI3K/AKT/mTOR pathway at the level of PI3K.

## 1.5 BACKGROUND ON NEOADJUVANT THERAPY IN 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 and Smith 2003; Scholl et al. 1994; Semiglazov et al. 2004; Fisher et al. 2012; Wolff and Davidson 2000). The randomized studies evaluating neoadjuvant therapy as well as meta-analyses of these studies have shown that neoadjuvant therapy can improve breast conservation rates, decreasing the number of women obligated to undergo mastectomy (Mieog et al. 2007; Fisher et al. 2012). 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). The concept of neoadjuvant therapy is now well established and a standard treatment option for patients with early breast cancer. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis was recently conducted evaluating over 12,000 patients treated with neoadjuvant chemotherapy as part of clinical trials (Cortazar et al. 2012). The results of this meta-analysis confirmed an association of pathologic complete response [pCR] with favorable long-term outcomes in high-risk populations (i.e., HER2-positive, high-grade hormone receptor positive and triple negative subtypes), although the magnitude of pCR improvement predictive of the long-term survival benefits could not be determined. In September 2013, the Food and Drug Administration (FDA) granted accelerated approval of Perjeta as part of a complete treatment regimen for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer in the neoadjuvant setting.

## 1.6 BACKGROUND ON GDC-0032

GDC-0032 is a potent selective inhibitor of Class I PI3K alpha, delta, and gamma isoforms, with 30-fold less potent inhibition of the beta isoform that is being developed as a therapy for human cancers. Nonclinical studies with GDC-0032 demonstrate that GDC-0032 inhibits proliferation of p110$\alpha$-mutant breast cell lines, inhibits tumor growth in human breast xenograft models harboring *PIK3CA* mutations, and results in a substantial reduction of PI3K pathway markers, including pAkt, pPRAS40, and pS6.

GDC-0032 has demonstrated activity in nonclinical models of *PIK3CA*-mutant breast tumors in vivo as a single agent and in combination with standard of care (e.g., paclitaxel or docetaxel) or endocrine therapies (e.g., letrozole or fulvestrant). GDC-0032 has a favorable in vitro and nonclinical in vivo absorption, distribution, metabolism, and elimination profile that has characteristics consistent with a compound that can be delivered orally to achieve clinical exposure similar to the nonclinical efficacy findings described herein. Additional studies, including 16-week toxicity studies in rats and dogs, phototoxicity studies, and an embryo-fetal development study, support the Phase II neoadjuvant trial with GDC-0032 in combination with endocrine therapy.

In vitro, single-agent GDC-0032 potency is also observed in cell lines that do not harbor *PIK3CA* mutations (Figure 1). In in vitro combination studies, the aromatase-expressing breast cancer cell line (MCF7X2.3.ARO) showed positive combination effects between GDC-0032 and endocrine therapies (see Figure 2). In this cell line, GDC-0032 alone caused growth inhibition (50% effective concentration [$EC_{50}$] = 95 nM). Effects on growth were also observed with letrozole and fulvestrant. Combined treatment of cells with GDC-0032 and letrozole caused dose-dependent inhibition of cell viability at lower concentrations of either GDC-0032 or letrozole resulting in enhanced activity for the combination. In addition, combination activity was demonstrated in the *PIK3CA* wild-type (WT) cell line ZR75-1 when GDC-0032 was added to either fulvestrant or tamoxifen endocrine therapies (combination with letrozole not available in this cell line). However, in vivo data in a *PIK3CA* WT model are not available, because these cell lines do not grow as xenografts.

**Figure 1 GDC-0032 Potency in Non-*PIK3CA* Mutant Breast Cancer Cell Lines**

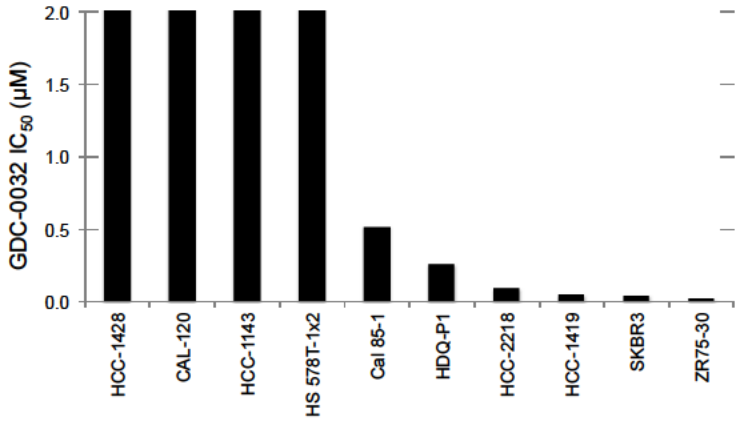
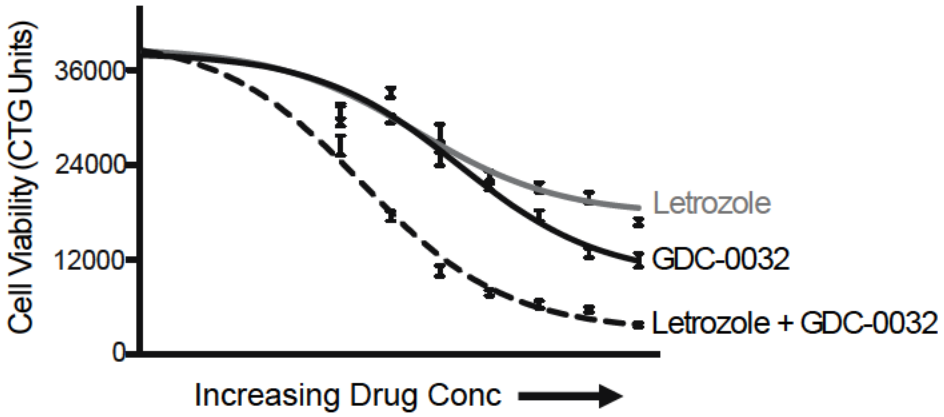


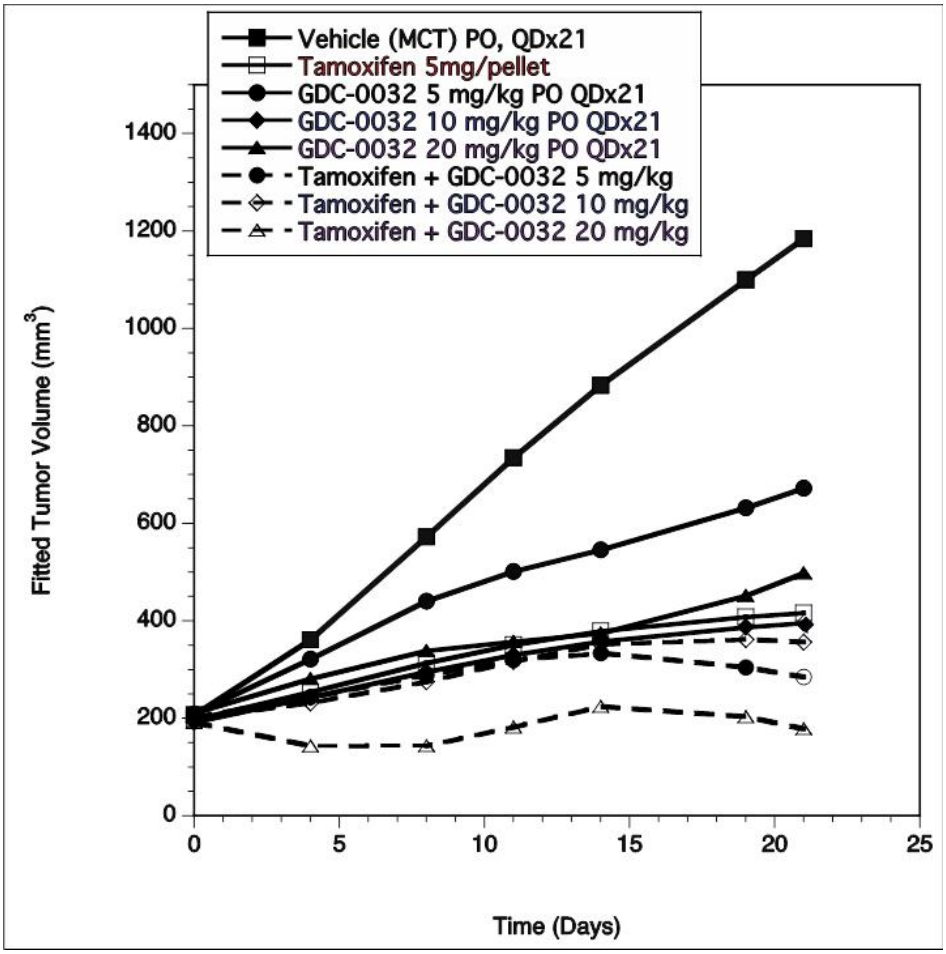

**Figure 2 Combination Effects between Letrozole and GDC-0032 in the Aromatase-Expressing MCF7.2x3 Breast Cancer Cell Line**




Conc = concentration.
MCF7X2.3.ARO (aromatase-expressing MCF7 cells) are sensitive to GDC-0032 in combination with endocrine therapies. Effects on viability are determined after 96 hours in culture.

Enhanced efficacy was demonstrated in combination with tamoxifen, another endocrine therapy used in the treatment of hormone receptor-positive advanced breast cancer. In this human MCF7-neo/HER2 (*PIK3CA* mutant [MT]) breast cancer xenograft model in immunocompromised nude (nu/nu) mice, administration of GDC-0032 at all doses tested (5, 10, or 20 mg/kg) in combination with tamoxifen (5-mg/pellet) resulted in greater efficacy (shown as a percentage of tumor growth inhibition [TGI]: 82% TGI, 80% TGI, and 102% TGI, respectively) compared to tamoxifen alone (73% TGI) or GDC-0032 as a single agent (71% TGI at 20 mg/kg) (see Figure 3). All combinations were well tolerated with no increase in mortality and no greater body weight loss than single agents alone.

**Figure 3 Efficacy of Tamoxifen in Combination with GDC-0032 in MCF7-Neo/Her2 Estrogen Receptor-Positive Mouse Xenografts**




QD = once daily; PO = oral gavage.

Vehicle was MCT (0.5% methycellulose/0.2% Tween-80).

Tamoxifen pellets (5 mg/pellet, 60-day release) were implanted on Day 0 of dosing (8 days post tumor implantation). Tumor volumes after QD oral administration of GDC-0032 for 21 days are depicted by dose group.

Please refer to the GDC-0032 Investigator's Brochure for additional nonclinical data for GDC-0032 supporting this clinical trial.

### 1.6.1 Toxicology

Please refer to the GDC-0032 Investigator's Brochure for details on the toxicology program to support this clinical trial.

## 1.7 SUMMARY OF CLINICAL DATA FOR GDC-0032

### 1.7.1 Clinical Safety Data with GDC-0032

As of 5 July 2013, a total of 144 patients have been treated with GDC-0032 either as single agent (90, 63%) or in combination with endocrine therapy (54, 37%).

GDC-0032 is currently in Phase I (Study PMT4979g). Study PMT4979g is an open-label, dose-escalation trial using a 3 + 3 design to assess the safety, tolerability, and pharmacokinetics of GDC-0032 administered orally daily for 28 days to patients with locally advanced or metastatic solid tumors and in combination with endocrine therapy in ER+ breast cancers. As of 5 July 2013, enrollment into the dose-escalation stage of Study PMT4979g had been completed with 34 patients enrolled at doses with a range of 3 to 16 mg daily. GDC-0032 was well tolerated in the first three cohorts (3, 5, and 8 mg), with no patients experiencing a dose-limiting toxicity (DLT). At the 16-mg dose level, 2 of the 11 safety-evaluable patients experienced a DLT (Grade 4 hyperglycemia and Grade 3 fatigue). At the 12-mg dose level, 1 of the 10 safety-evaluable patients experienced a DLT of Grade 3 acute renal failure. Although the single-agent GDC-0032 maximum tolerated dose (MTD) was not exceeded at the 16-mg dose level, the recommended GDC-0032 dose and schedule for the single-agent expansion cohorts is 9 mg daily on the basis of long-term safety data through multiple treatment cycles. As of the cutoff date, a total of 53 patients have been enrolled in the 9-mg daily dosing expansion cohorts.

As of 5 July 2013, adverse events that occurred in ≥ 10% of the 87 patients treated with daily single-agent GDC-0032 and were assessed as related to GDC-0032 were as follows: diarrhea (47%), hyperglycemia (38%), nausea (36%), fatigue (34.5%), decreased appetite (31%), rash (16%), stomatitis (13%), vomiting (13%), and mucosal inflammation (11.5%). Study–drug-related Grade 3 and 4 adverse events included hyperglycemia (9.4%), colitis (7.5%), pneumonitis (3.8%), rash (including maculopapular rash with or without itching, redness, and peeling) 5.7%, asymptomatic increased aminotransferase levels in the blood (1.9%), anemia (1.9%), increase in blood creatinine (1.9%), diarrhea (1.9%), fatigue (1.9%), hypokalemia (1.9%), hypophosphatemia (1.9%), pneumonia (1.9%) and stomatitis (1.9%).

As of 5 July 2013, a total of 27 patients have been enrolled in the expansion cohort of GDC-0032 at dose levels of 6 and 9 mg daily (19 patients at 6 mg, and 8 patients at 9 mg) daily in combination with letrozole (Cohort E). No DLTs were observed at either dose level. Adverse events that occurred in ≥ 10% of the 27 safety-evaluable patients assessed as related to GDC-0032 were diarrhea (67%), fatigue (30%), nausea (30%), decreased appetite (26%), hyperglycemia (26%), stomatitis (26%), dysgeusia (22%), mucosal inflammation (18.5%), rash (18.5%), asthenia (15%), pruritis (15%), vomiting (15%), dry mouth (11%), dry skin (11%) and muscle spasms (11%). Study – drug-related Grade 3 and 4 adverse events included diarrhea (11%), mucosal inflammation (7.4%), increased amylase in the blood (3.7%), increased aspartate aminotransferase (AST) in

the blood (3.7%), increased alkaline phosphate in the blood (3.7%), fatigue (3.7%), increased gamma-glutamyltransferase in the blood (3.7%), hyperglycemia (3.7%), hypokalemia (3.7%), increased lipase in the blood (3.7%), papilloedema (3.7%) and stomatitis (3.7%).

As of 5 July 2013, a total of 27 patients have been enrolled in the expansion cohort of GDC-0032 at dose levels of 6 and 9 mg daily (21 patients at 6 mg and 6 patients at 9 mg) in combination with fulvestrant (Cohort F). No DLTs were observed at either dose level. One patient has been enrolled in the Phase II part of the study with 6 mg GDC-0032 in combination with fulvestrant. Adverse events that occurred in $\geq$ 10% of the 27 patients and were assessed as related to GDC-0032 were diarrhea (46%), hyperglycemia (32%), nausea (32%), decreased appetite (25%), fatigue (25%), rash (21%), stomatitis (21%), asthenia (18%), muscle spasms (14%), vomiting (14%), dysgeusia (11%), gastroesophageal reflux disease (11%) and mucosal inflammation (11%). Study–drug-related Grade 3 and 4 adverse events included hyperglycemia (14%), diarrhea (7%), dyspnea (4%), flank pain (4%), hyponatremia (4%), neutropenia (4%), rash (4%) and vomiting (4%).

Please refer to the GDC-0032 Investigator's Brochure for additional information.

#### 1.7.1.1 Preliminary Pharmacokinetics

Pharmacokinetic (PK) data are available from 34 patients treated with GDC-0032 at 3, 5, 8, 12, and 16 mg in the ongoing Phase I/II clinical trial (Study PMT4979g). The cohort mean apparent clearance and the terminal half-life ($t_{1/2}$) following a single, oral dose of GDC-0032 had a range of 4.77–9.17 L/hour and 36.7–43.8 hours, respectively. Following daily oral dosing for 8 days, there was a 2- to 4-fold accumulation of GDC-0032. The pharmacokinetics of GDC-0032 appears to be dose linear and time-independent. Preliminary PK data from Cohort E suggest there is no drug-drug interaction (DDI) between letrozole plus GDC-0032. Mean plasma exposure of letrozole when given in combination with GDC-0032 (maximum concentration observed [$C_{max}$] = 0.407 μM and area under the concentration–time curve from 0 to 24 hours [$AUC_{0-24}$] = 8.01 μM*hr) was comparable with the historical single-agent exposure ($C_{max}$ = 0.495 μM and $AUC_{0-24}$ = 10.1 μM*hr) (Awada et al. 2008). Similarly, plasma concentrations of GDC-0032, when given in combination with letrozole, were within the range predicted by the population PK model. Therefore, letrozole plus GDC-0032 can be co-administered without the risk of a DDI.

GDC-0032 was metabolized primarily by CYP3A4 in human liver microsomes (HLMs) and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low to moderate potential to induce CYP3A4, preliminary data from the Phase I/II study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore,

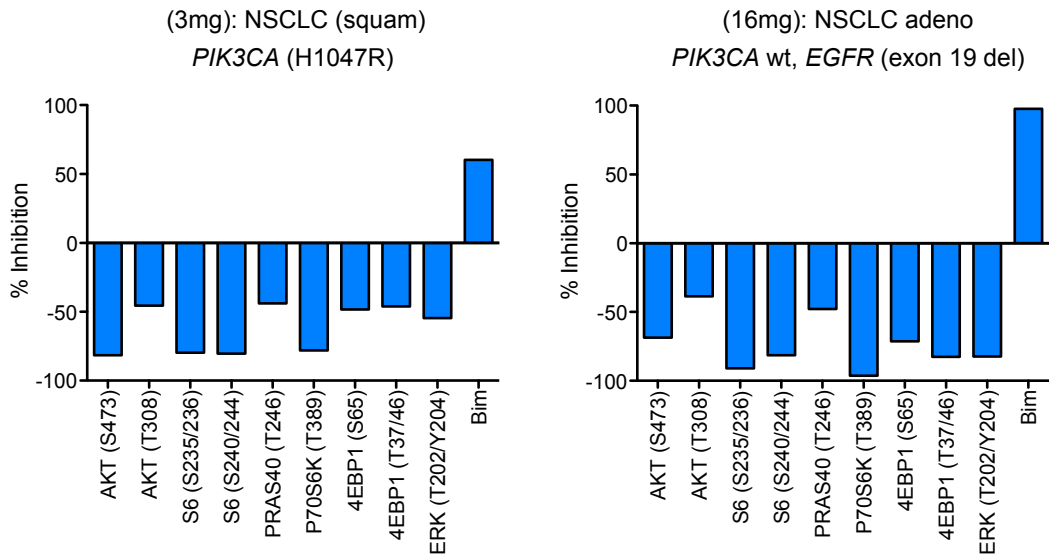
GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a PK DDI.

For additional details, refer to the GDC-0032 Investigator's Brochure.

### 1.7.1.2 Preliminary Pharmacodynamics

Paired tumor biopsies were obtained from both *PIK3CA* MT and *PIK3CA* WT non-small cell lung cancer (NSCLC) patients treated at either the 3-mg or 16-mg GDC-0032 dose level, respectively, at screening (pretreatment biopsy) and during Cycle 1 in Study PMT4979g (on-treatment biopsy). Inhibition of PI3K pathway markers, including decreases of >60% in pAKT and pS6 (compared with baseline), were demonstrated in these patients' paired tumor biopsies (see Figure 4).

**Figure 4 Decrease in PI3K Pathway Activation in Tumor Biopsies Observed upon GDC-0032 Treatment in Both *PIK3CA* MT and WT Tumors**




MT = mutant; NSCLC = non – small-cell lung cancer; WT = wild type.

As of 5 July 2013, metabolic partial responses via FDG-PET (≥20% decrease in maximum standardized uptake value) were observed in 23 out of 38 patients assessed (61%) and included patients from the lowest dose tested (3 mg). Thirteen of these 23 were breast cancer patients. Of the 13 response-evaluable patients treated with GDC-0032 plus letrozole, 10 patients (77%) had a partial metabolic response. Of the 15 response-evaluable patients treated with GDC-0032 plus fulvestrant, 11 (73%) had a partial metabolic response.

For additional details, refer to the GDC-0032 Investigator's Brochure.

## 1.8 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Cancer is one of the leading causes of death worldwide, with solid tumors accounting for the majority of these deaths. An estimated 1.38 million women across the world were diagnosed with breast cancer in 2008, accounting for 23% of all cancers diagnosed in women. Breast cancer is the most common cause of death from cancer in women worldwide, estimated to be responsible for almost 460,000 deaths in 2008 (Ferlay et al. 2010).

A neoadjuvant study in a similar patient population with the combination of letrozole and the mTOR inhibitor everolimus has already been completed (Baselga et al. 2009). Please refer to Sections 1.4, 1.5, and 3.3 for further rationale supporting the proposed trial design of combining GDC-0032 with letrozole in the neoadjuvant setting for this patient population. In postmenopausal women with hormone receptor-positive metastatic breast cancer, it is hypothesized that the combination of decreasing estrogen levels with letrozole and inhibition of the PI3K pathway with GDC-0032 may have improved anti-tumor activity as compared to endocrine therapy alone. This is supported by the nonclinical and clinical data outlined below.

GDC-0032 is a potent, selective small molecule inhibitor of Class 1 PI3K that is being developed by Roche/Genentech as an anti-cancer therapeutic agent. Activating and transforming mutations in the p110 alpha subunit of PI3K are commonly found in tumors. GDC-0032 has been shown to be a potent inhibitor of growth in various human cancer cell lines, and especially in nonclinical models of *PIK3CA* MT tumors. In addition, combination activity was demonstrated in the *PIK3CA* WT cell line ZR75-1 when GDC-0032 was added to either fulvestrant or tamoxifen endocrine therapies (combination with letrozole not available in this cell line).

GDC-0032 has also shown additive efficacy in combination with endocrine therapy in a hormone receptor-positive breast cancer xenograft model as outlined in Section 1.6. Nonclinical data support the investigation of GDC-0032 as a single-agent in solid tumors and in combination with endocrine therapy in patients with hormone receptor-positive, advanced breast cancer.

Available clinical data with single-agent GDC-0032 suggest that GDC-0032 has dose-linear pharmacokinetics with a half-life of approximately 37−44 hours. Pharmacodynamic markers of PI3K pathway inhibition upon treatment with GDC-0032 have been observed. These include decreases in phospho-S6 in platelet-rich plasma and decreases in F- flurodeoxyglucose-positron emission tomography uptake. Available clinical data also include multiple confirmed partial responses in patients treated with GDC-0032. These include a patient with *PIK3CA* MT lung adenocarcinoma treated at the 3 mg daily dose and another patient with *PIK3CA* MT, hormone receptor-positive, HER2-positive metastatic breast cancer treated at the 5 mg daily dose. In addition, a

patient with *PIK3CA* WT lung cancer treated at the 3 mg daily dose has had prolonged stable disease and remained on study for over 11 months. These data show that single-agent GDC-0032 doses below 6 mg have been shown to have anti-tumor activity. These aggregate data support the use of 6 mg in combination with letrozole.

Letrozole is a marketed product that is approved in the European Union (E.U.) and the United States (U.S.) for the treatment of hormone receptor-positive breast cancer. Based upon the different mechanisms of action of GDC-0032 and the well-established safety profile of letrozole, there are no expected overlapping, significant toxicities between letrozole and GDC-0032.

As of 5 July 2013, efficacy data are available for 24 patients treated with GDC-0032 in combination with letrozole; 3 patients (12.5%) had a partial response as best overall response, 2 of which were confirmed partial responses (cPRs) (1 cPR at 6 mg; 1 cPR at 9 mg). Of the 25 efficacy-evaluable patients treated with GDC-0032 in combination with fulvestrant, 7 patients (28%) had a partial response as best overall response, of which 3 were cPRs (1 cPR at 6 mg; 1 partial response at 9 mg). cPRs have been observed in both *PIK3CA* mutant and *PIK3CA* WT breast cancer patients. Maintenance of cPR has been observed in a patient who had a dose reduction from 6 mg to 3 mg for an adverse event. In addition, no additional safety concerns have been observed with GDC-0032 in combination with letrozole in the ongoing Phase I study compared to GDC-0032 given as single agent.

A number of clinically appropriate strategies to minimize risk to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, protocol design, and management guidelines. These will also be clearly highlighted and discussed in detail at investigator meetings and site visits. In addition, please refer to the GDC-0032 Investigator's Brochure for details regarding potential risks, associated precautions, and other relevant nonclinical and clinical safety information.

Due to the need to develop improved therapies to reverse or delay resistance to current endocrine therapy in HER2-negative, hormone receptor-positive breast cancer and on the basis of the clinical and nonclinical data available for GDC-0032, Genentech/Roche feels that the risk-benefit profile of GDC-0032 in combination with letrozole in postmenopausal patients with HER2-negative, hormone receptor-positive early stage breast cancer is favorable for proceeding with the proposed randomized Phase II clinical trial.

# 2. OBJECTIVES

## 2.1 EFFICACY OBJECTIVES

The primary objective of this study is to evaluate the efficacy of letrozole plus GDC-0032 versus letrozole plus placebo in women with ER+/HER2- early stage breast cancer, as measured by the following co-primary endpoints:

- Tumor overall objective response rate (ORR) by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in all enrolled patients and *PIK3CA* MT patients
- pCR rate in breast and axilla (ypT0/Tis ypN0) by local evaluation in all enrolled patients and *PIK3CA* MT patients

The secondary efficacy objectives of this study are the following:

- Tumor ORR, assessed by centrally assessed breast MRI via modified Response Evaluation Criteria in Solid Tumors (RECIST) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR ypT0/Tis ypN0) by local evaluation in *PIK3CA* WT patients
- The following secondary objectives will be performed in all enrolled patients and separated by *PIK3CA* mutation status:
- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of locally assessed ORR using the following methods:
    - Breast ultrasound
    - Clinical breast exam (i.e., palpation)
    - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally assessed, preoperative endocrine prognostic index (PEPI) score upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo.
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment.
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

## 2.2 SAFETY OBJECTIVES

- The safety objective for this study is as follows:
- Evaluate the safety of letrozole plus GDC-0032 versus letrozole plus placebo

## 2.3 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for this study are as follows:

- Evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23)

## 2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess whether biomarkers from tumor tissue or blood, including but not limited to somatic cancer associated mutations, PTEN expression, pro-survival pathways (such as PI3K/AKT, MAPK etc.), apoptotic markers, hormone receptor expression levels, and levels of RNA and DNA expression are predictive of response
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to anti-tumor activity
- To assess concordance and percentage of *PIK3CA* mutation status from baseline biopsy and surgical specimen
- To assess emergence of resistance alleles from tumor tissue or blood
- To assess concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response
- To assess the pharmacokinetics and possible drug interaction between letrozole and GDC-0032 upon concomitant administration
- To assess the correlation of GDC-0032 drug levels and GDC-0032 related response (efficacy or adverse events [e.g., colitis, rash])
- To assess the influence of pharmacogenetic polymorphisms on GDC-0032 and/or letrozole on pharmacokinetics and response (either efficacy and/or adverse events)
- Compare the rates of breast-conserving surgery (BCS) and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo.

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF STUDY

This is a two-arm, randomized, double-blind, multicenter, pre-operative study to evaluate the effect of combining letrozole and GDC-0032 versus letrozole and placebo in postmenopausal women with ER+/HER2- untreated, Stage I-III operable breast cancer whose primary tumors are $\geq$ 2 cm. Patients with cT4 or cN3 tumors are not eligible.

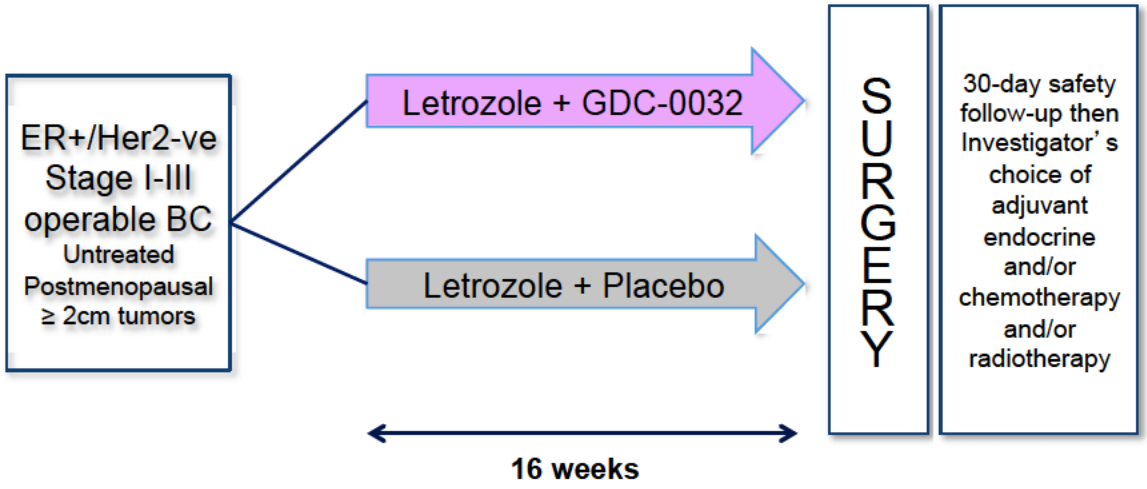
Standard of care assessments/procedures (e.g., bilateral mammogram) performed within 28 days of Day 1 dosing do not need to be repeated for screening purposes.

All patients will undergo pretreatment tumor tissue acquisition (snap-frozen [optimal cutting temperature; OCT] and formalin-fixed paraffin-embedded cores [FFPE]). Two pretreatment FFPE core biopsies and one freshly frozen core biopsy must be obtained for all patients prior to beginning study drug treatment. Tumor tissue from prior diagnostic FFPE core biopsies may be used for enrollment eligibility purposes. For the purpose of enrollment, ER, progesterone receptor (PR), and HER2 will be locally determined prior to beginning of study treatment. Remaining tissue will be retained for future translational studies. Pre-surgical sentinel lymph node biopsy (SLNB) is not allowed.

Patients will be randomized into one of the two treatment arms with a 1:1 randomization ratio. Letrozole at 2.5 mg will be dosed once daily plus either GDC-0032 at 6 mg or placebo on a 5 – days-on/ 2 – days-off schedule for a total of 16 weeks (see Figure 5). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

**Figure 5 Study Schema**

Letrozole 2.5 mg QD + GDC-0032 6 mg or placebo QD on a 5 – days-on/2 – days-off schedule




| | Pretreatment | Day 15 (Week 3) | Week 9 | Week 16 | Surgery (Week 17-18) |
|---|---|---|---|---|---|
| Tumor tissue | ● | ● | | | ● |
| MRI | ● | | ● | ● | |
| Breast U/S | ● | | ● | ● | |
| Mammogram | ● | | | ● | |

BC = breast cancer; ER + = estrogen receptor positive; MRI = magnetic resonance imaging; QD = once daily; U/S = ultrasound.

After confirmation of all the eligibility criteria, patients will be randomized to one of the treatment arms. A second biopsy will be performed on Day 15 (Week 3) for biomarker analyses. Biopsies should be performed at least 2 hours after GDC-0032 dose administration.

Randomization will be stratified according to 2 factors:

1. Tumor size (T1-T2 vs. T3)
2. Nodal status (cytologically positive vs. radiologically or cytologically negative)

The study will enroll approximately 330 patients at approximately 110 global sites.

At Weeks 1, 5, 9, 13, and 16 the primary breast tumor and axillary lymph nodes will be assessed by clinical breast examination (palpation and caliper measurement). Suspicion of progression based on clinical exam at any time should be further evaluated (Figure 6).

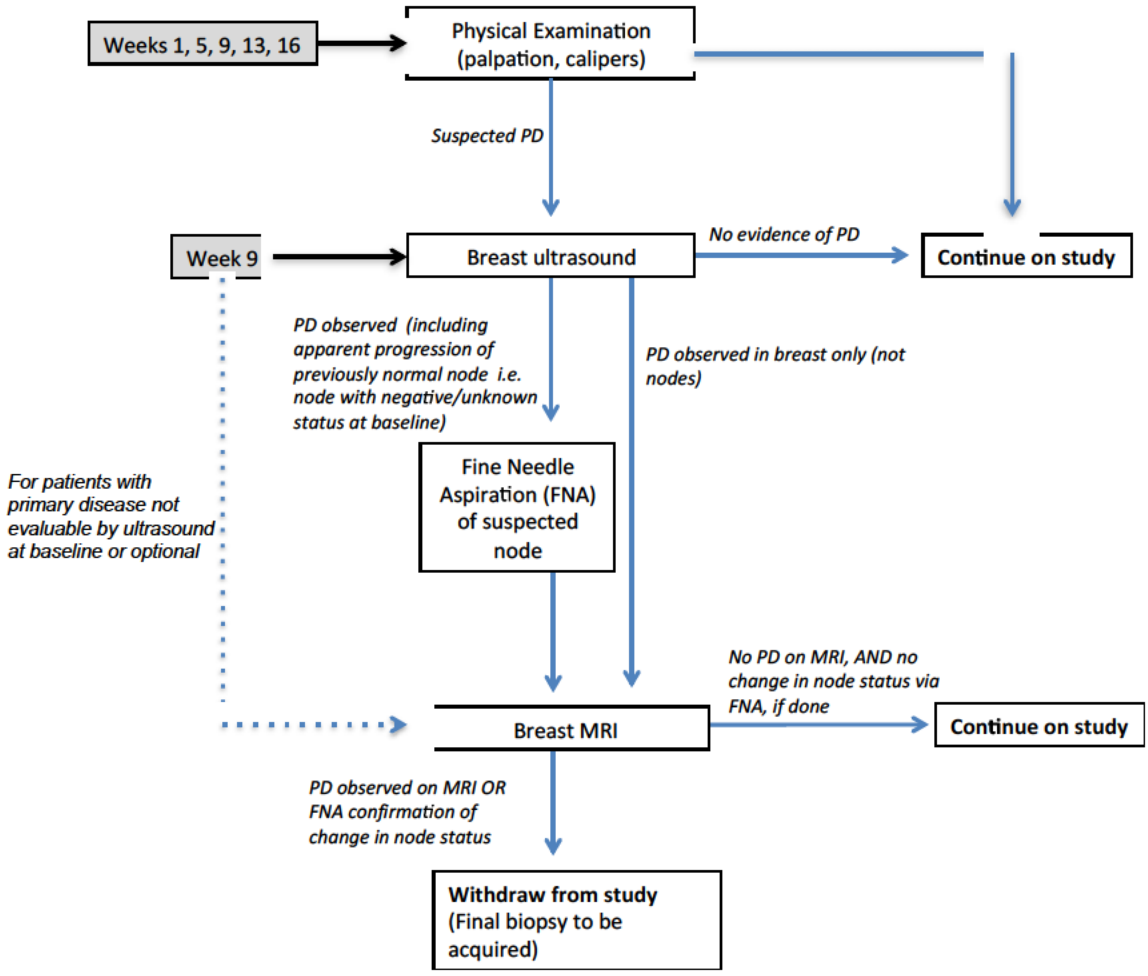
At Week 9, a breast ultrasound will be performed to ensure that there is no progressive disease and for the purpose of surgery planning. Suspicion of progressive disease on breast ultrasound should be confirmed by investigator-assessed breast MRI. Patients with primary disease not evaluable by ultrasound at baseline should be assessed by MRI at Week 9. Suspected progression in nodes should also be confirmed by fine needle aspiration (FNA) if these nodes had not been previously shown to be cytologically positive for cancer. Patients with progressive disease (as defined by modified RECIST, Appendix 3), can either proceed directly to surgery or be taken off of the study, according to the investigator's decision. If the patient goes off-study, every reasonable effort should be made to obtain a new biopsy prior to beginning another systemic treatment.

From Week 13, the patient will visit with the surgeon. The purpose of this visit is two-fold: tentative planning of the type of breast surgery to be performed (breast conservative vs. mastectomy) and scheduling the date for definitive surgery.

During Week 16, breast MRI will be done for the purpose of primary endpoint analysis. Clinical breast exam, breast ultrasound, and mammography will also be conducted prior to surgery for the purpose of the secondary endpoint analysis.

Blood sample for exploratory endpoint analysis will be collected at screening, at Week 3, and prior to surgery.

**Figure 6 Schematic Representing Confirmation of Progression**




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

### 3.1.1 Surgery

Surgery will take place after at least 16 weeks of treatment, during Weeks 17 – 18. Surgery should be performed within 4 days after the last dose of GDC-0032, if possible, to best observe pharmacodynamic knockdown with GDC-0032 in the surgical specimen. Surgery may be delayed due to toxicity or other safety issues, upon discussion with the Medical Monitor (see Section 5.4.1) or recommendations from the Independent Data Monitoring Committee (IDMC; see below). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

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. Surgery specimens will be collected for histological examination to assess for pCR and for other endpoint analyses.

Following surgery, follow-up will proceed according to local standards of care. Adjuvant endocrine therapy and/or chemotherapy will be delivered as per the investigator's choice. Postoperative radiotherapy is required if BCS is performed. In the event of mastectomy, radiotherapy is to be administered according to local guidelines.

A postsurgery visit will be performed 4 weeks (+ 1 week) after surgery, and will mark the end of the study. Assessment of adverse events and general safety will be collected at this visit and the plan for future treatment will be recorded.

The patient should be evaluated at baseline and after Week 13 of treatment for planning of the surgical procedure (BCS or mastectomy), and both physician recommendation and final patient decision should be documented in the electronic Case Report Form (eCRF).

The co-primary efficacy endpoint, pCR (pCR–ypT0/is, ypN0) will be established via a local review following completion of neoadjuvant therapy and surgery.

Please refer to the pathology manual for further guidance of evaluation for pCR and directions for sending a copy of the pathology report.

A schedule of assessments is provided in Appendix 1.

An Independent Review Facility (IRF) will be used to determine the tumor ORR via MRI. IRF procedures are detailed in the IRF charter.

### 3.1.2 Independent Data Monitoring Committee

An IDMC will monitor accumulating patient safety data at a minimum of once every 6 months until the last patient has completed study treatment. Additional details (e.g., IDMC members, communication, affiliations) will be provided in the IDMC charter.

The IDMC will convene for an interim safety analysis to evaluate safety and pharmacokinetics after the first 20 patients have completed surgery and have had 30 days of follow-up. The IDMC will create and review unblinded, pooled summaries of the safety and available PK summaries (all interim analyses). While this review is being conducted, patient accrual into the study will continue. The Medical Monitor may also request additional safety analysis and may call for additional meetings of the IDMC to review ongoing safety data.

The IDMC will share results from interim safety analyses with the study team. The study team will share interim safety results with study investigators as needed for the conduct of the study and the safety of the patients. Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections.

## 3.2 END OF STUDY

The end of the study is defined as the date when the last patient has her postsurgery visit. The total duration of the study is expected to be approximately 24 months for enrollment, plus 5.5 months after last patient in.

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Conducting the Study in the Neoadjuvant Setting

Breast cancer is a heterogeneous disease, and not every breast tumor responds equally to a specific agent. Studies based on global gene expression analyses have provided additional insights into this complex scenario. Over the past 10 years, four major classes of breast cancer (Luminal A, Luminal B, HER2-enriched, and Basal-like) and a Normal Breast-like group have been identified and intensively studied (Perou et al. 2000; Sørlie et al. 2001). Known as the intrinsic subtypes of breast cancer, these groups of tumors have revealed critical differences in incidence, survival, and response to treatment. As genomic studies evolve, further sub-classifications of breast tumors are expected to emerge. Thus, a major challenge in breast cancer management is how to prospectively select patients who will derive the maximum benefit from a given drug regimen, minimizing unnecessary toxicities for patients with non-responsive disease.

Neoadjuvant therapy, a systemic therapy administered prior to breast cancer surgery, is now widely used in the 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, especially those with larger tumors. The tumor may shrink prior to surgery, thus increasing the rate of BCS (Coudert et al. 2006), and since the response to therapy can be monitored, the patient might be also spared further treatment with inactive medications.

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 treatment response at a biological level. Finally, the surgical specimen, if pCR is not reached, can be utilized as well. 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 (von Minckwitz and Fontanella 2013; Cortazar et al. 2012).

### 3.3.2 Rationale for Patient Population

Postmenopausal patients with HER2-negative, ER+, early stage breast cancer will be enrolled in this study. This patient population is usually treated with a combination of surgery, anti-hormonal therapy and/or chemotherapy, according to staging and biological features.

Recently, everolimus was approved by the FDA and European Medicines Agency in combination with exemestane for the treatment of advanced or metastatic breast cancer in patients after recurrence or progression following treatment with nonsteroidal AIs. In the neoadjuvant setting, a combination of letrozole and everolimus resulted in improved responses over letrozole alone in patients with ER+ breast cancer (Baselga et al. 2009).

Important findings in trials with drugs targeting mTOR, like everolimus, produce a pharmacodynamic paradox: while inhibiting mTOR, they lead to an upregulation of the pAKT, resulting in feedback PI3K/AKT/mTOR pathway activation (Tabernero et al. 2009). This finding suggests that alternative pharmacologic strategies to shut down the pathway upstream of AKT should be pursued. One of these strategies is to inhibit the PI3K/AKT/mTOR pathway at the PI3K level. PI3K-inhibitors are central regulators of the mTOR signaling pathway, and nonclinical findings show that PI3K-inhibitors and dual PI3K-mTOR inhibitors induce a greater amount of apoptosis than everolimus in estrogen-deprived in vitro models (Sanchez et al. 2011); therefore, it is hypothesized that PI3K-inhibitors may be active and demonstrate greater anti-tumor activity as compared to AIs alone in the neoadjuvant setting.

### 3.3.3 Rationale for Control Group

Aromatase inhibitors (AIs) have been found to be more effective than tamoxifen as a neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer.

Several trials have assessed the efficacy and safety of neoadjuvant endocrine therapy using AIs in patients with postmenopausal breast cancer (Eiermann et al. 2001; Smith et al. 2005; Ellis et al. 2011).

The P024 trial was a worldwide, prospective, randomized, multicenter trial that randomized 337 postmenopausal patients with ER$+$ breast cancer to receive either 4 months of neoadjuvant letrozole or tamoxifen (Eiermann et al. 2001). The primary endpoint of P024 was the percentage of patients in each treatment arm with objective response as determined by clinical palpation. Secondary endpoints included ORR determined by mammogram and ultrasound, and included the percentage of patients in each arm who had become eligible for BCS. The trial demonstrated a significantly higher clinical response rate for letrozole when compared to tamoxifen (55% vs. 36%; $p < 0.001$) in the intent-to-treat (ITT) population. An improved ORR for letrozole was also observed with ultrasound (35% vs. 25%; $p < 0.042$) and mammogram (34% vs. 16%; $p < 0.001$). The higher response rate assessed by clinical palpation translated into a significantly higher rate of women undergoing BCS in tumors that had initially been considered unsuitable for this procedure (45% vs. 35%; $p = 0.022$). Median time-to-response was 66 days in the letrozole group and 70 days in the tamoxifen group, and both treatments were well tolerated.

The IMPACT trial was a randomized, Phase II, double-blind, double-dummy, multicenter trial that randomly assigned 330 postmenopausal women with ER+ operable or locally

advanced, potentially operable breast cancer in a 1:1:1 ratio to receive a daily dose of anastrozole 1 mg and tamoxifen placebo, tamoxifen 20 mg and anastrozole placebo, or a combination of tamoxifen 20 mg and anastrozole 1 mg for 12 weeks before surgery. The tumor ORR was assessed by both caliper and ultrasound. No significant differences in ORR in the ITT population between patients receiving tamoxifen, anastrozole, or the combination were seen. However, in a predefined analysis, there was a nonsignificant trend towards more patients requiring mastectomy at baseline actually receiving BCS with anastrozole than with tamoxifen (44% vs. 31%, respectively; $p = 0.23$); this difference became significant for patients deemed by their surgeon to be eligible for BCS after treatment (46% vs. 22%, respectively; $p = 0.03$). All treatments were well tolerated.

The ACOSOG Z1031 trial compared three AIs in a randomized, Phase II, neoadjuvant trial designed to select agents for Phase III investigations. Three hundred seventy-seven postmenopausal women with clinical Stage II to III ER+ breast cancer were randomly assigned to receive neoadjuvant exemestane, letrozole, or anastrozole. The primary endpoint was clinical response. No formal comparison between arms was pre-specified in the statistical plan. ORR was 62.9%, 74.8%, and 69.1% for the exemestane, letrozole and anastrozole arms, respectively. On the basis of clinical response rates, letrozole and anastrozole were selected for further investigation; however, no other differences in surgical outcome, PEPI score, or Ki67 suppression were detected. The BCS rate for mastectomy-only patients at presentation was 51%.

Results from these trials suggest that neoadjuvant endocrine therapy can be beneficial in postmenopausal patients with hormone-sensitive breast cancer, and that it offers an alternative to neoadjuvant chemotherapy.

### 3.3.4 Rationale for the Efficacy Outcome Measure of Response Rate Assessed by Magnetic Resonance Imaging

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, non-registrational, neoadjuvant trials in combination with endocrine therapy (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 computed tomography (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 (Akazawa et al. 2006; Balu-Maestro et al. 2002; Yeh et al. 2005), including the I-SPY trial (Hylton et al. 2012). For these reasons, ORR as assessed by breast MRI has been chosen as a co-primary endpoint for this trial.

#### 3.3.4.1 Rationale for Efficacy Outcome Measure of Pathologic Complete Response

pCR is a recognized efficacy endpoint of neoadjuvant trials, especially those with neoadjuvant chemotherapy, as it has been correlated with long-term outcomes, such as event-free survival (von Minckwitz and Fontanella 2013).

In trials of neoadjuvant hormonal therapy, pCR is an unlikely event. For instance, in the neoadjuvant trial comparing everolimus plus letrozole to letrozole, pCR rates were 1.4% and 0.8%, respectively (Baselga et al. 2009).

In the ongoing Phase I/II trial that combines letrozole with GDC-0032, tumor shrinkage has been observed, and some patients presented sustained partial responses. As pCR is a recognized indicator of activity to a given regimen, it would be useful to assess it as a co-primary efficacy endpoint of this trial. Furthermore, for the same trial size, this would represent a minimal increase in the minimum detected difference (MDD) of the co-primary endpoint for pCR ORR (from MDD of 12% to MDD of 13%).

In September of 2013, the FDA granted accelerated approval of Perjeta as part of a complete treatment regimen for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer in the neoadjuvant setting.

#### 3.3.4.2 Rationale for Ki67 Measurements

Ki67 is a well-established proliferation biomarker with prognostic value in ER+ breast cancer (Dowsett et al. 2011). Efficacy of endocrine therapy relies on induction of cell-cycle arrest, and during neoadjuvant treatment, Ki67 levels reflect the ability of endocrine agents to suppress proliferation (Smith et al. 2005; Ellis et al. 2011). In the neoadjuvant trial of letrozole with everolimus, by using the definition that patients with natural log (Ki67) $< 1$ at Day 15 have an antiproliferative response, 57% of everolimus-treated patients were responders vs. 30% in the placebo arm, with a significant p value of $< 0.01$ (Baselga et al. 2009). Furthermore, the mean reduction in the percentage of Ki67-positive tumor cells at Day 15 relative to baseline was greater in the everolimus-treated patients ($90.7\% \pm 3.2\%$) than in the placebo group ($74.8\% \pm 6.8\%$; $p = 0.0002$). In the IMPACT trial, Ki67 was assessed at baseline, on Day 15, and at surgery (Smith et al. 2005). For each treatment arm, the reduction in geometric mean Ki67 levels was significantly higher for anastrozole than for tamoxifen at both time points ($p = 0.004$, $p = 0.001$, respectively), but no differences were found between tamoxifen and the combination. In the ASCOSOG Z1031 trial (Ellis et al. 2011), although no data on Ki67 at Day 15 were available, no differences were found between treatments at baseline and at surgery (after $16 - 18$ weeks of therapy). The geometric mean percentage change in Ki67 for each treatment was similar between the arms (anastrozole 78%, exemestane 81.2%, and letrozole 87.1%).

The issue of whether Ki67 decrease at surgery or at any timepoint during treatment correlates with long-term efficacy outcomes has been addressed in the P024 trial

(Eiermann et al. 2001). Treatment with letrozole led to higher, treatment-induced reduction of Ki67 levels in the tumor at surgery (87% reduction in the letrozole arm vs. 75% in the tamoxifen arm; analysis of covariance $p = 0.0009$) based on the 185 specimens with available data on Ki67 (Ellis et al. 2003). With a median follow-up of 61.2 months, low levels of Ki67 in the biopsy at the end of treatment were significantly associated with better relapse-free survival (RFS; HR 1.4 per natural log increase in the Ki67 value, 95% CI $1.2 - 1.6$, $p < 0.001$), and breast cancer specific survival (HR 1.4, 95% CI $1.1 - 1.7$, $p = 0.009$). Finally, in the IMPACT trial, higher Ki67 expression after 2 weeks of endocrine therapy was statistically significantly associated with lower RFS ($p = 0.004$), whereas higher Ki67 expression at baseline was not (Smith et al. 2005).

Importantly, the Ki67 suppression in these hormonal neoadjuvant trials mirrored efficacy outcomes in large adjuvant trials: adjuvant BIG1-98 trial ($n = 8,010$) showed the superior efficacy of letrozole over tamoxifen (Regan et al. 2011), similar to the neoadjuvant P024 trial ($n = 185$); the adjuvant ATAC trial ($n = 9,366$) showed that anastrozole was better than tamoxifen and the combination of anastrozole plus tamoxifen (Cuzick et al. 2010), similar to neoadjuvant IMPACT ($n = 259$); and the adjuvant MA27 trial ($n = 7,576$) showed similar efficacy of anastrozole and exemestane (Goss et al. 2013), mirroring neoadjuvant ACOSOG Z1031 ($n = 266$). These results suggest that a biological superiority hypothesis generated by a neoadjuvant study may help the design of future adjuvant hormonal therapy trials.

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

#### 3.3.4.3 Rationale for Using the Preoperative Endocrine Prognostic Index Score

In addition to Ki67, pathologic tumor size (T1 or T2 versus T3 or T4), node status (positive or negative), and the ER status (positive Allred score 3–8 versus negative Allred score 0–2) of the surgery specimen were also determined to have independent prognostic value for relapse and death after relapse in the P024 trial (Ellis et al. 2008). A PEPI score, prognostic for RFS, which weighs each of these factors according to their associated hazard ratios, was developed and subsequently validated in an independent data set from the IMPACT trial (Ellis et al. 2008). No relapses were recorded in either trial in patients with tumors classified as T1N0 and with a PEPI score of 0 (residual tumor with a Ki67 level $\leq 2.7\%$, and with maintained ER expression) or in the rare patient with a pCR.

In this trial, the PEPI score will be assessed centrally.

#### 3.3.4.4 Rationale for Assessing ORR by Clinical Breast Exam (Palpation), Mammography, and Breast Ultrasound

Objective overall response rate will also be assessed by clinical breast exam, mammography, and breast ultrasound during screening and prior to surgery. These data will allow for more direct comparison of results to other neoadjuvant trials with endocrine therapy as described in Section 3.3.3. The concurrent acquisition of ORR data with these techniques, in addition to MRI-based measures, will also provide valuable comparative information on these methods, which will be important for both future neoadjuvant studies and GDC-0032 clinical development.

#### 3.3.4.5 Rationale for Assessing Enhancing Tumor Volume by Breast Magnetic Resonance Imaging

As shown in the I-SPY trial, tumor volume measurements based on the percent of tumor with enhancing signal after contrast agent administration may be a more sensitive measure of response during neoadjuvant treatment than longest dimension measures (Hylton et al. 2012). However, there are no established response criteria for volumetric data, and the extrapolation of current one- and two-dimensional criteria to volumetric data based on a spherical model may not be appropriate given the range of tumor morphologies expected in this population of patients (Loo et al. 2011). Additionally, there are only very limited data on the clinical relevance of any particular range in change in tumor volume during the course of neoadjuvant treatment. For these reasons, changes in enhancing tumor volume as measured by breast MRI will be a secondary endpoint in the trial.

### 3.3.5 Rationale for Independent Review Facility

Due to the relatively novel nature of using MRI as an imaging endpoint, a central assessment by an IRF for the co-primary endpoint of response rate via MRI will be performed to ensure consistency across all sites participating in the study.

### 3.3.6 Rationale for Interim Safety Review

The first 20 patients will be assessed for safety following surgery and 30 days beyond. This will allow the IDMC to review all safety data during the treatment period and to evaluate any surgery complications that may be attributed to GDC-0032.

### 3.3.7 Rationale for GDC-0032 Dosage

As of 5 July 2013, 34 patients have been enrolled into the dose-escalation stage of Study PMT4979g, and 56 patients have been enrolled into the single-agent expansion cohorts at 9 mg in Stage 2 (Cohorts A-D and G). Five dose-escalation cohorts (i.e., 3, 5, 8, 12, and 16 mg daily) were tested. The maximal administered dose was 16 mg. To obtain more safety data on long-term tolerability, the recommended single-agent dose and schedule for the single-agent GDC-0032 expansion stage is 9 mg daily.

In Study PMT4979g, as of the 5 July 2013 data cutoff date, there were 87 safety evaluable patients treated with single-agent GDC-0032 (3 – 16 mg daily). A total of 97%

of patients experienced at least one adverse event per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 (NCI CTCAE v4.0). The most frequently reported adverse events, occurring in ≥10% safety-evaluable patients regardless of causality, were diarrhea (55%), fatigue (49%), nausea (47%), decreased appetite (39%), hyperglycemia (38%), vomiting (28%), dizziness (22%), rash (22%), dyspnea (18%), hypokalemia (18%), pyrexia (17%), cough (16%), anemia (13%), dehydration (13%), headache (13%), stomatitis (13%), AST increased (12%), mucosal inflammation (12%) and pruritis (10%).

As of 5 July 2013, 54 patients have been treated with GDC-0032 in combination with endocrine therapy with either letrozole (Cohort E) or fulvestrant (Cohort F) at either 6 mg or 9 mg dose levels. No DLTs were observed during dose escalation in either Cohorts E or F. Expansion cohorts at the 6-mg dose level were enrolled to obtain more safety data on long-term tolerability. Fifty (93%) of the 54 safety-evaluable patients experienced at least one adverse event that was assessed as related to GDC-0032.

Of the 54 patients, 17 patients were treated with GDC-0032 plus letrozole. Adverse events that occurred in ≥10% of patients that were assessed as related to GDC-0032 (6mg and 9mg) were diarrhea (67%), nausea (33%), fatigue (30%), rash (30%), hyperglycemia (26%), decreased appetite (26%), stomatitis (26%), dysgeusia (22%), mucosal inflammation (19%), asthenia (15%), vomiting (15%), pruritis (15%), muscle spasms (11%), dry skin (11%), and dry mouth (11%).

Of the 19 efficacy-evaluable patients treated with GDC-0032 in combination with letrozole, one patient at 6 mg had a cPR. The *PIK3CA* mutation status of this patient is unknown. Since efficacy has been observed at 6 mg, and the long-term safety suggests that 6 mg is better tolerated, the neoadjuvant study will utilize 6 mg GDC-0032 in combination with letrozole.

Of the 27 efficacy-evaluable patients treated with GDC-0032 in combination with fulvestrant, 2 confirmed partial responses were observed at 6 mg and 1 confirmed partial response at 9 mg.

Colitis has been observed with an incidence rate of 6.2% (10/160 patients). The time (from the first dose of study treatment) to onset of colitis ranged from approximately 82 – 248 days as either a single agent or in combination with letrozole or fulvestrant. Most of the colitis cases have been observed at the 9-mg dose level or higher. Most of the colitis cases have been observed at the 9-mg dose level or higher. To mitigate the late-onset adverse events, such as colitis, an intermittent dosing schedule will be applied. With the 40-hour half-life, a limited impact on efficacy is anticipated. PK modeling has shown that a schedule of 5 days on/2 days off will maintain GDC-0032 drug exposure levels within an efficacious range as assessed by various breast cancer cell lines. There has also been data presented for another PI3K inhibitor BKM120 with a similar half-life in combination with letrozole in a Phase Ib study that demonstrated improved tolerability

with similar efficacy for a schedule of 5 days on/2 days off as compared to daily continuous dosing of the PI3K inhibitor (Mayer et al. 2012).

### 3.3.8 Rationale for Biomarker Assessments

Breast cancer is a heterogeneous disease, and *PIK3CA* mutations have been shown to vary among patients (CGAN 2012). Therefore, all patients may not equally likely benefit from treatment with GDC-0032. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with *PIK3CA*-driven pathogenesis who are most likely to respond to GDC-0032. Pharmacodynamic biomarkers will be assessed to assess the biologic activity of the addition of GDC-0032 to letrozole.

It has been suggested that not all molecular alterations in the PI3K/AKT/mTOR pathway result in pathway activation. In a comprehensive analysis of tumors from 850 breast cancer patients, protein markers of PI3K/AKT/mTOR pathway activation (pAKT, pS6, and p4EBP1) correlated strongly with *INPP4B* and PTEN loss, to a degree with *PIK3CA* amplification, but were not elevated in *PIK3CA*- MT luminal A cancers (CGAN 2012). This apparent disconnect between the presence of *PIK3CA* mutations and biomarkers of pathway activation had been previously noted (Loi et al. 2010), and stress the need to find innovative and robust predictive biomarkers to PI3K/AKT/mTOR pathway inhibiting agents (Saini et al. 2013).

Next generation sequencing (NGS) techniques, like deep genome sequencing, may offer a unique opportunity to identify such biomarkers of response. For example, using whole genome sequencing, a two base-pair deletion in the *TSC1* gene was found in a metastatic bladder cancer patient with a prolonged response ($>2$ years) to everolimus as single agent (Iyer et al. 2012). Among 13 additional bladder cancer patients treated with everolimus in the same trial, those with *TSC1* mutant tumors remained on therapy longer than those with WT tumors (7.7 vs. 2.0 months, $p=0.004$), suggesting that mTORC-1 directed therapies may be most effective in cancer patients whose tumors harbor *TSC1* somatic mutations. Similar approaches could be of great value when analyzing responses to agents targeting the PI3K/AKT/mTOR pathway, especially in the neoadjuvant setting.

In addition to mutational activation of proteins, levels of RNA and DNA can also activate the PI3K pathway. For example, increases in DNA copy number in receptor tyrosine kinases such as FGFR1/2 and IGF-1R, which occur at some frequency in breast cancer, can activate downstream PI3K pathway. Hormone receptor positive breast cancer can be divided into luminal A and luminal B subtype, with the luminal B subtype displaying a higher proliferative index. Therefore, profiling the RNA and DNA expression of tumors will allow intrinsic subtyping of patients enrolled onto study. In addition, PI3K transcription activation signatures may identify additional patients who could respond to PI3K inhibitors outside of *PIK3CA* mutations.

The use of circulating tumor DNA (ctDNA) to monitor response to treatment is an area of great interest. It could allow for an early, non-invasive, and quantifiable method for use in the clinical setting to identify candidates for specific therapies and monitoring of disease mutation status over time (Higgins et al. 2012). The neoadjuvant setting is ideal to prospectively test these approaches.

### 3.3.9 Rationale for Day 15 Biopsy

On-study biopsies can provide valuable information regarding target engagement and downstream pathway suppression. Assessing how GDC-0032 interacts with letrozole in this previously untreated patient population provides a unique opportunity to understand the interaction between two anti-cancer molecules. When available, FFPE tumor samples will be assessed for pathway modulation using immunohistochemistry (IHC) methodologies, and fresh frozen OCT samples will be assessed using reverse phase protein array (RPPA) technologies, or equivalent. Measurement of Ki67 after 2 weeks of continuous letrozole and GDC-0032 combination treatment versus letrozole and placebo will give a good benchmark to prior neoadjuvant studies that demonstrated a larger decrease in Ki67 at this 2-week timepoint for a combination of letrozole and everolimus as compared to letrozole and placebo (Baselga et al. 2009). This Day 15 biopsy will also be useful in identifying potential biomarkers that may help predict a tumor response for patients treated with GDC-0032.

### 3.3.10 Rationale for Collection of Blood Sample for the Detection of Plasma Protein Biomarkers

Emerging evidence indicates that increases in levels of systemic cytokines and chemokines, such as receptor tyrosine kinase growth factors, can attenuate response to drugs, particularly targeted agents such as GDC-0032 (Wilson et al. 2012). Assays to assess the expression of soluble, systemic cytokines and chemokines from the plasma of patients will be carried out using ELISA-based mass spectrometry or equivalent methodologies.

### 3.3.11 Rationale for Collection of Blood Sample for DNA Sequencing to Identify Mutations in Plasma

There is increasing evidence that circulating DNA obtained from blood specimens of cancer patients is representative of the DNA and mutational status of tumor cells (Diehl et al. 2008; Maheswaran et al. 2008). Assays are available that can detect the major PI3K mutations (and other cancer-related genes) in plasma, and results from this analysis will be correlated with tumor specimens.

### 3.3.12 Rationale for Collection of Blood Sample for Next Generation Sequencing

Next generation sequencing (NGS) technologies generate a large quantity of sequencing data. Tumor DNA can contain both reported and unreported chromosomal alterations due to tumorigenesis process. To help control for sequencing calls in

previously unreported genomic alterations, a normal blood sample will be taken during pre-screening to determine whether the alteration is somatic or germline.

### 3.3.13 Rationale for Pharmacokinetic Sample Collection Schedule

PK samples will be collected from early breast cancer patients in this study to assess the pharmacokinetics of GDC-0032 and possible DDI between letrozole and GDC-0032 in this population. Considering the lack of DDI between GDC-0032 and letrozole upon concomitant administration in the 24 metastatic breast cancer patients in the Phase I study (preliminary data), this drug interaction in early breast cancer patients is unlikely. Hence, extensive PK sample collection is not needed; sparse PK sampling from patients enrolled in this study is adequate. The proposed PK sample collection schedule will also enable assessment of a concentration and response relationship to better understand the following: pharmacokinetics/pharmacodynamics (efficacy), PK/safety correlation, and population pharmacokinetics. Additional PK samples may be collected for safety concerns (e.g., severe adverse event) in order to better characterize drug levels in these patients at the time of the adverse event.

### 3.3.14 Rationale for the Collection of DNA for Exploratory Pharmacogenetic Polymorphisms

One sample (approximately 3 mL of whole blood) will be collected from all patients using K3-EDTA collection tubes. Samples will be used for the evaluation of genetic polymorphisms of drug metabolic enzymes including, but not limited to, CYP2C9, CYP3A4/5, and UGT1A1, and transporters (e.g., OATP1B1) and for genetic variants which could contribute to potentially drug-related rash and/or colitis safety assessments (including but not limited to human leukocyte antigen [HLA]). For sample handling procedures, storage conditions, and shipment instructions, see the laboratory manual. Only in circumstances where there is concern for collection of this genetic material for above evaluations, can this assessment be considered not mandatory as part of study assessments in this study. Results of any analyses from these samples will be reported outside the clinical study report.

It is established that genetic variants of drug-metabolizing enzymes and transporters can affect the pharmacokinetics of drugs, which affects their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1, which facilitates the metabolism and excretion of SN 38 (the active metabolite of irinotecan), are at higher risk for adverse effects associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006). Preliminary results from in vitro metabolism studies with GDC-0032 suggest that they are partially metabolized by multiple Phase I cytochrome P450 enzymes, including CYP3A4. Although in vitro studies can help elucidate the roles of enzymes in the metabolism of the drug, these results are not always predictive of in vivo metabolism for a number of reasons, such as differences in drug concentrations that the enzymes encounter in vitro and in vivo. For this reason, a blood sample for DNA isolation is proposed to be

collected from all patients in this study for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics or response to GDC-0032. The decision to analyze the samples will be based on a review of the pharmacokinetics and response data. Most recently, the role of HLA has been demonstrated to play an important role in the development of drug-induced rash for some drugs (carbamazepine, abacavir, and allopurinol). Therefore, evaluation of genetic variants of genes that may regulate the immune response (including but not limited to HLA) may also be investigated to characterize unusual safety responses that are not predicted by GDC-0032 pharmacokinetics.

The analysis will be performed on identifiable DNA samples, because it is necessary to link a patient's PK data with genotype. This analysis would be restricted to the evaluation of genes that may be involved in the pharmacokinetics of GDC-0032, drug metabolism, disposition, or elimination and/or response of patients who develop severe adverse reactions such as colitis or rash. Samples may be stored and analyzed up to 15 years after the completion of the study, at which time all DNA samples collected for this analysis will be destroyed.

### 3.3.15 Rationale for Patient-Reported Outcome Assessments

A PRO is "any report on the status of a patient's health condition that comes directly from the patient, without any interpretation of the patient's response by a clinician or anyone else" (FDA Guidance for Industry 2007). PRO measures are able to contextualize a patient's experience on trial, elucidating symptom and treatment burden. Since early breast cancer is often asymptomatic, the PRO objective is to evaluate and compare PROs of treatment-related symptoms, patient functioning, and the health-related quality of life between treatment arms (Lemieux et al. 2011).

The EORTC QLQ-C30 and associated breast cancer module, QLQ-BR23, were selected because they were specifically developed to assess the most salient constructs and experiences with breast cancer and its treatment. The EORTC QLQ-C30 is a widely and frequently used PRO measure in oncology trials that contains a global health status scale, functional scales (physical, role, emotional, cognitive, and social), and general cancer symptom scales/items with a recall period of 'the past week.'

The second measure, the QLQ-BR23, is a breast cancer specific modular supplement to the EORTC QLQ-C30, and includes additional functioning scales and symptom scales/items relating to breast cancer.

These instruments demonstrate strong psychometric properties, of both reliability and validity, and meet the requirements for this study (EORTC QLQ-C30 Scoring Manual, 1999). Therefore, PRO data will be collected from patients using the EORTC QLQ-C30 and modified QLQ-BR23 (Quinten et al. 2009).

## 3.4 OUTCOME MEASURES

### 3.4.1 Efficacy Outcome Measures

#### 3.4.1.1 Co-Primary Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

- Tumor ORR, via centrally assessed breast MRI via modified RECIST (Appendix 3) in all enrolled patients and *PIK3CA* MT patients.
- pCR rate in breast and axilla (total pCR) as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system (Appendix 6) by local evaluation in all enrolled patients and *PIK3CA* MT patients.

#### 3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Tumor ORR, assessed by centrally assessed breast MRI via modified RECIST (Appendix 3) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR) by local evaluation in *PIK3CA* WT patients.

The following secondary outcome measures will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of ORR, as measured by modified RECIST criteria (Appendix 3) using the following methods:
    - Breast ultrasound
    - Clinical breast exam (i.e., palpation)
    - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally assessed PEPI score upon treatment with letrozole plus GDC-0032 with letrozole plus placebo
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) yoT0/is, ypNX (breast pCR)

### 3.4.2 Safety Outcome Measures

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE, v4.0
- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Serious adverse events

- Protocol-defined adverse events of special interest
- Clinically significant changes in vital signs and in clinical laboratory results during the adverse event reporting period (see Section 5.3.1)

### 3.4.3 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- HRQoL, including side-effects of therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems), and patient functioning as measured using the EORTC QLQ–C30 and the modified breast cancer module QLQ–BR23

### 3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- ORR, pCR rate, and PEPI scores according to the decrease in Ki67 after 2 weeks of letrozole plus GDC-0032 and letrozole plus placebo.
- Expression of biomarkers before, during, and after therapy. These include, but are not limited to, the following:
    - PI3K pathway aberrations
    - Gene signatures, including intrinsic subtyping and PI3K pathway activity
    - Hormone receptor expression levels
    - Protein and phospho-protein markers and combinations
    - Mutations within cancer-associated genes
    - Copy number alterations in cancer-related genes
    - Plasma-based protein biomarkers
    - ctDNA
- Compare the rates of BCS and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo
- The relationship between GDC-0032 concentration and tumor response and/or drug safety response
- Letrozole concentrations with and without administration of GDC-0032
- The relationship between pharmacogenetic differences in drug metabolizing enzymes and transporters and other patient-specific covariates with PK of GDC-0032 or letrozole and/or drug response
- Changes from baseline to surgery in the apparent diffusion coefficient (ADC), a marker of tumor cellularity derived from diffusion-weighted MRI
- Concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response

# 4. MATERIALS AND METHODS

## 4.1 PATIENTS

Patients for this study include postmenopausal patients with ER+/HER2- untreated, Stage I-III operable breast cancer. The size of the primary tumor should be ≥2 cm by MRI.

### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF) prior to any study-specific procedure
- Female patients
- Postmenopausal status and age ≥18 years. Postmenopausal status is defined as follows:
  - Age ≥ 60 years or
  - Age < 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment or
  - Prior bilateral oophorectomy (≥ 28 days prior to Day 1 of treatment)
- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor ≥ 2 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 ≥ 2 cm and designated as the "target" lesion for all subsequent tumor evaluations.
  - Stage I to operable Stage III breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms).
- ER-positive and HER2-negative breast cancer, as per local laboratory or regional definition
- Breast cancer eligible for primary surgery
- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for *PIK3CA* mutation status by central histopathology laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Fasting glucose ≤125 mg/dL
- Adequate hematological, renal, and hepatic function, as follows:
  - Absolute neutrophil count ≥ 1500/μL
  - Platelets count ≥100,000/μL

  - Hemoglobin $\geq$ 9 g/dL
  - Serum bilirubin $\leq 1.5\times$ the upper limit of normal (ULN)
  - Patients with known Gilbert's disease who have serum bilirubin $\leq 3 \times$ ULN may be enrolled
- Aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase $\leq 1.5 \times$ ULN
- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation:

  $(140 - \text{age}) \times (\text{weight in kg}) \times (0.85)$
  $72 \times (\text{serum creatinine in mg/dL})$
- International normalized ratio (INR) $< 1.5 \times$ upper limit of normal (ULN) and activated partial thromboplastin time (aPTT) $< 1.5 \times$ ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2–3 is required. If anticoagulation is required for a prosthetic heart valve, then INR should be between 2.5–3.5.
- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Ability and willingness to comply with study visits, treatment, testing, and to comply with the protocol, in the investigator's judgment

### 4.1.2 Exclusion Criteria

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

- Any prior treatment for primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer
- 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 sentinel lymph node biopsy prior to study treatment
- *Patients for whom upfront chemotherapy is clinically judged appropriate as optimal neoadjuvant treatment*
- *Patients for whom immediate surgery is indicated*
- Type 1 or 2 diabetes requiring antihyperglycemic medication
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteric absorption

- History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis)
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF)> 470 msec
- *DLCO < 60% of the predicted values (see Appendix 7 for calculations)*
- Clinically significant (i.e., active) cardiovascular disease, like uncontrolled hypertension, unstable angina, history of myocardial infarction, cardiac failure class II-IV (New York Heart Association, Appendix 5), or any other that in the judgment of the investigator could jeopardize patient safety or study outcomes
- 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
- Active infection requiring intravenous (IV) antibiotics
- Patients requiring any daily supplemental oxygen
- Clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis
- Known human immunodeficiency virus (HIV) infection
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications
- Significant traumatic injury within 3 weeks prior to initiation of study treatment
- Major surgical procedure within 4 weeks prior to initiation of study treatment
- Inability to comply with study and follow-up procedures
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

### 4.2.1 Patient Randomization

After written informed consent has been obtained and eligibility has been established, the study site will obtain a patient's identification number and treatment assignment using a permuted block randomization algorithm via an interactive voice or web-based response system (IxRS).

### 4.2.2 Stratification

Patients will be randomized into one of the two treatment arms in a 1:1 ratio based on the following stratification factors:

- Tumor size (T1-2 vs. T3)
- Nodal status (cytologically positive vs. radiologically or cytologically negative). If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then fine needle aspiration (FNA) or core biopsy is required to confirm nodal status.

### 4.2.3 Blinding

Investigators and patients will be blinded to treatment assignment of GDC-0032 or placebo.

*For emergency situations,* the investigator will be able to break the treatment code by contacting the IxRS. *The responsibility to break the treatment code in emergency situations resides solely with* the *investigator. For non-emergency situations, the investigator needs to obtain approval from* the Medical Monitor *to break* the *treatment code.* Unblinding during the study will result in the withdrawal of a patient from the study. For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected, suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. The PK assay group will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed and bioanalytical methodology to employ. However, the PK scientist does not have access to the PK assay results and therefore stays blinded until the PK assay results need to be interpreted and reported. Samples from patients assigned to the comparator arm will be analyzed for letrozole. However, GDC-0032 assay will be analyzed by request (i.e., to evaluate a possible error in dosing).

## 4.3 STUDY TREATMENT

### 4.3.1 Formulation, Packaging, and Handling

#### 4.3.1.1 GDC-0032 and Placebo

GDC-0032 Drug Substance and Drug Product are manufactured according to current Good Manufacturing Practice guidelines for use in the clinical studies. Each lot of GDC-0032 for clinical studies is subjected to a series of quality control tests to confirm its identity, purity, potency, and quality.

GDC-0032 is provided for use in clinical studies as a white, film-coated, immediate-release tablet formulation of 3 mg strength. The tablet formulation consists of GDC-0032 active, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and Opadry 2 white film coating. All excipients used in the formulation are compendial (USP/NF/Ph. Eur/JP) grade with the exception of the film-coating. The film-coating consists of polyvinyl alcohol-part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc, and these ingredients are compendial.

Placebo tablets will be identical in shape and color to the 3-mg tablets of GDC-0032 and will be indistinguishable from the 3-mg tablets of GDC-0032. The ingredients in the placebo tablets are identical to those in the 3-mg tablets of GDC-0032, except for the absence of GDC-0032 active.

The GDC-0032 active and placebo tablets are packaged in high-density polyethylene bottles, are labeled for clinical use, and should not be stored above 25°C.

For further details, see the GDC-0032 Investigator's Brochure.

#### 4.3.1.2 Letrozole

Letrozole will be labeled according to regulatory requirements in each country, as well as in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and will be labeled for investigational use only. The Sponsor will provide letrozole free of charge to all study sites.

Refer to the letrozole (e.g., Femara®) Package Insert or summary of product characteristics (SmPC) for details on the formulation and storage of letrozole.

### 4.3.2 Dosage, Administration, and Compliance

#### 4.3.2.1 GDC-0032 and Placebo

Patients will receive an oral, daily dose of 6 mg GDC-0032 or placebo on a schedule of 5 days on/2 days off for a maximum of 16 weeks. Patients will take GDC-0032 at the same time of day ± 2 hours, unless otherwise instructed. Patients will be instructed as to the number of tablets to take. Patients will be asked to record the time and date that they take each dose in a medication diary.

Unless otherwise instructed, GDC-0032 or placebo should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal).

If a patient misses a GDC-0032 or placebo dose or vomits up a tablet, she should be instructed to skip that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up. Patients will be instructed to bring their medication diary to each study visit for assessment of compliance. Patients will also be instructed to bring all unused tablets to each study visit for GDC-0032 or placebo accountability.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

#### 4.3.2.2 Letrozole

Patients will receive an oral, daily dose of 2.5 mg letrozole for 16 weeks (or until time of surgery at the investigator's discretion). No dose modifications of letrozole are permitted. Any overdose or incorrect administration of letrozole should be noted on the letrozole Administration eCRF. Adverse events associated with an overdose or incorrect administration of letrozole 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 (letrozole and GDC-0032) will be provided by the Sponsor where required by local health authority regulations. The investigational site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) 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 GDC-0032

The Sponsor will offer post-trial access to the study drug (GDC-0032, letrozole, or other study interventions) 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 would not 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 untreated, postmenopausal ER+/HER2−, early stage, operable breast cancer
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for untreated, postmenopausal postmenopausal ER+/HER2−, early stage, operable breast cancer
- 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
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 7 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

GDC-0032 was metabolized primarily by CYP3A4 in HLM and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low-to-moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a pharmacokinetic DDI.

Letrozole is mainly metabolized to a pharmacologically inactive carbinol metabolite by CYP2A6 and CYP3A4 in vivo. GDC-0032, which has the potential to induce CYP3A4 based on in vitro induction studies, was administered in combination with letrozole in the expansion phase of Study PMT4979g to assess their DDI potential. Preliminary data from 10 patients in this cohort indicated that steady state plasma concentrations of both letrozole and GDC-0032, following once daily administration of the combination (2.5 mg letrozole plus 6 or 9 mg GDC-0032), were similar to historical, single-agent data suggesting lack of DDI between GDC-0032 and letrozole. These preliminary results suggest that GDC-0032 and letrozole combination may be administered without the risk of a pharmacokinetic DDI.

In vitro CYP inhibition studies in HLMs and induction studies in human hepatocytes suggested a low to moderate potential of GDC-0032 to perpetrate DDIs. A clinical DDI study with rifampin (CYP3A4 inducer) and itraconazole (CYP3A4 inhibitor), to understand the effect of CYP inhibitors or inducers on the pharmacokinetics of GDC-0032, is currently ongoing (Study GP28617).

### 4.4.2 Prohibited Therapy

Prohibited therapy is as follows:

- **Anti-cancer therapy:** No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than letrozole permitted in this protocol) will be allowed.
- **Hormone replacement therapy**, **topical estrogens (including any intra-vaginal preparations), hormonal contraception, megestrol acetate, and selective estrogen-receptor modulators used with prophylactic intent**: If a patient is receiving these at the moment of registration, treatment should be discontinued prior to randomization.
- **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.
- **Potent CYP3A4 inhibitors:** Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole and itraconazole) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If a strong CYP3A4 inhibitor is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.
- ***Potent CYP3A4 inducers:*** *Concomitant use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, phenobarbital) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to induce CYP3A4. If a strong CYP3A4 inducer is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.*

## 4.5 STUDY ASSESSMENTS

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

### 4.5.1 Informed Consent Forms and Screening Log

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

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

### 4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases that are currently active or that were active within the previous 5 years, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 15 days prior to the screening visit.

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

### 4.5.3 Physical Examination

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems as well as weight and height (height is measured at the screening visit only). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examination may be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

### 4.5.4 Vital Signs

Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

### 4.5.5 Electrocardiograms

Triplicate electrocardiogram (ECG) recordings will be obtained at each specified timepoint (see the schedule of assessments in Appendix 1).

### 4.5.6 Distant Sites Tumor Assessment

Baseline distant sites tumor staging procedures should be performed in alignment with National Comprehensive Cancer Network (NCCN) or national guidelines, within 28 days prior to randomization.

As a reference, as per NCCN guidelines, staging procedures are based on clinical stage:

- 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.
- For Stage IIIB and Stage IIIC: bone scan and CT of chest, abdomen, and pelvis should be conducted for all patients.

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.

### 4.5.7 Tumor and Response Evaluations

All measurable disease must be documented at screening and reassessed at subsequent timepoints as outlined in Appendix 1. Responses based on clinical breast exam, breast ultrasound, and mammography will be investigator-assessed. Whenever possible, assessments should be performed by the same evaluator to ensure internal consistency across visits. Response via breast MRI will be centrally assessed, and all assessments will be based on modified RECIST criteria (see Appendix 3).

**Clinical Breast Examination:** Assessment of primary breast tumor and regional lymph nodes must be done by physical examination (palpation) during baseline evaluation, Weeks 1, 5, 9, 13 and 16 during the treatment phase, and prior to surgery. Breast tumor measurement by caliper (preferred) or rule 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.

**Mammogram:** Bilateral mammograms must be obtained at baseline within 28 days prior to enrollment and again prior to surgery. Mammographic tumor measurements are to be recorded in the eCRF.

**Breast Ultrasound:** Bilateral breast ultrasounds must be obtained at baseline within 28 days prior to enrollment. Investigator decision whether to perform unilateral or bilateral ultrasounds performed at Week 9 and prior to surgery (Week 16) may be unilateral or bilateral and per investigator discretion. If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then FNA or

core biopsy is required. Sonographic tumor measurements are to be recorded in the eCRF. The tumor site may be marked with a radiopaque clip or marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy.

**Breast MRI:** Contrast-enhanced breast MRI scans will be mandatory for all study patients at baseline (within 28 days prior to enrollment) and prior to surgery (Week 16). MRI is optional at Week 9, but will be mandatory if a primary breast lesion is not evaluable by ultrasound, or if there are signs of disease progression on the Week 9 ultrasound (see Figure 6).

Breast MRI scans should not be acquired within 48 hours after biopsy, and the 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 as assessed by the central reading facility, the scan may be repeated, at least 48 hours after the first scan before the start of study treatment. Other MRI acquisition sequences, such as diffusion-weighted imaging, may be acquired during this study during the MRI scan visits for each patient. Additional MRI-derived metrics such as ADC value may provide additional insight into changes in tumor cellular composition.

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

### 4.5.8 Surgical Treatment Plan

The planned and actual surgical treatment (BCS or mastectomy) performed should be documented and reported in the eCRF. Patients should be reassessed after completion of neoadjuvant therapy and prior to surgery.

### 4.5.9 Surgical Specimen – Pathology

The co-primary endpoint of the study (pCR) will be as identified by local pathology review. Guidelines regarding pathology specimen preparation, labeling and review are outlined in the pathology manual.

### 4.5.10 Laboratory Assessments

The following assessments will be performed at the local laboratory. The frequency of assessments is provided in Appendix 1.

- Hematology (complete blood count, including red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with differential [neutrophils, eosinophils, basophils, lymphocytes, monocytes, and other cells]), and platelet count.
- Coagulation (INR and aPTT/PTT)

- Fasting serum chemistry (blood urea nitrogen [BUN], creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, ALT), performed following $\geq$10-hour fast
- Fasting lipid profile and amylase (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides, amylase, and lipase) performed following a $\geq$10 hour fast
- Fasting insulin and glucose
- Glycosylated hemoglobin ($HbA_{1c}$)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)

The following assessments will be performed at a central laboratory. Instruction manuals outlining sampling procedures, storage conditions, and shipment instructions and supply kits will be provided for all central laboratory assessments:

- Mandatory tumor tissue
- 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 *PIK3CA* mutation testing as well as for other protocol-mandated exploratory assessments at baseline, Day 15, and at surgery.
- Tumor tissue should be of good quality based on total and viable tumor content. Evaluation of the patient's tumor sample for adequate tumor tissue content by a central laboratory must occur prior to initiation of study treatment. A minimum of ten unstained slides from a prior diagnostic FFPE core biopsy would be required for enrollment eligibility purposes.

  Two formalin-fixed, paraffin-embedded core needle biopsies and one freshly frozen OCT core needle biopsy are required at baseline and Day 15 (Week 3).

  A formalin-fixed, paraffin-embedded tumor block from surgical resection (Weeks 17 – 18) is required. If a tumor block cannot be obtained for various reasons (e.g., the tumor tissue is not sufficient at surgical resection), the site should discuss with the central study team. In such cases, paraffin-embedded, unstained slides (a minimum of 20 and up to 40 unstained slides) from a surgical specimen are required at surgery (Weeks 17 – 18).

  The specimens will be used for confirmatory central laboratory assessment of *PIK3CA* mutation status, Ki67, PTEN, ER/PgR and HER2 expression. In addition, other exploratory assessments, including but not limited to, PI3K signaling pathways may be evaluated, including protein expression and molecular profiling studies such as NGS and gene-expression.
- Plasma samples for exploratory research on candidate biomarkers include, but are not limited, to the following: ctDNA and plasma protein biomarkers

- Blood for NGS (if approved by local regulatory authorities)
- Blood for pharmacogenomics (if approved by local regulatory authorities)
- PK assessment

  Plasma samples will be collected to measure letrozole and GDC-0032 concentrations (see 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.

### 4.5.11 Assay Methods

#### 4.5.11.1 Mutational Analysis for *PIK3CA*

The *PIK3CA* mutation assay will be performed by a central laboratory.

Somatic mutations in the *PIK3CA* gene are found in approximately 35%–40% of ER-positive breast cancers and occur most commonly in Exons 9 and 20 in the codons encoding amino acids E542, E545, and H1047 (Saal et al. 2005). Real-time polymerase chain reaction (RT-PCR) assays that amplify exons that are commonly mutated in *PIK3CA* offer a sensitive and quantitative method to detect mutations from a tumor specimen. DNA will be extracted from tumor samples and subjected to allele-specific PCR assays that detect the WT allele, as well as to assays for nucleotide substitutions that include, but are not limited to, the following amino acid changes: R88Q, N345K, C420R, E542K, E545K/A/G/D, E546K/E/R/L, M1043I, H1047R/L/Y, H1049R. Following histopathological review, samples with $<$10% tumor content may not be evaluable for the *PIK3CA* assay. Samples will be run on cobas z480 analyzer, and *PIK3CA* mutation status (mutant or WT) will be made using appropriate cutoffs and automated software.

A designation of *PIK3CA* status unknown will be assigned to a sample wherein any one of the predefined mutations was not conclusively assessed.

#### 4.5.11.2 Pharmacodynamic Biomarker Assays in Tumor Tissues

Ki67 antigen is an important cell cycle-related nuclear protein that is expressed by proliferating cells in all phases of the active cell cycle (G1, S, G2, and M phase). As such, it is a useful marker of the proliferative state of a tumor. Ki67 protein levels will be determined by IHC through the use of standard techniques.

PI3K pathway, and other pro-survival, biomarkers will be tested in the fresh tumor biopsies by IHC, including, but not limited to, phospho-S6, phospho-AKT, phospho-4EBP1, and phospho-ERK. If tissue quantity permits, change in expression of pathway biomarkers will be measured by the RPPA using OCT fixed tissue. The basis of the technology is to immobilize small amounts of lysate from a tumor biopsy sample in serial dilution on a microarray slide. Multiple samples are thus arrayed on a slide and can be probed with antibodies that detect a particular phospho-epitope. Using this technology, we will profile approximately 80 key signaling nodes representing a number

of pathways known to be dysregulated in cancer, including receptors in the HER family, multiple components of PI3K/mTor signaling, as well as key members of the RAS/MAP kinase pathway.

#### 4.5.11.3 Analysis of Phosphatase Tensin Homolog Expression

PTEN status will be examined by IHC using a protocol that has been validated for specificity using several available cell line controls at a central laboratory. Tumor specimen will be scored only if appropriate staining is observed in internal control stromal or normal (non-tumor) tissue elements.

#### 4.5.11.4 Confirmation of Estrogen Receptor, Progesterone Receptor, and HER2 Status

ER, PR, and HER2 status will be determined at a central laboratory according to the American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) guidelines.

#### 4.5.11.5 Circulating Tumor DNA Analysis

ctDNA will be extracted from plasma samples collected from patients and used for the detection of oncogenic mutations using appropriate technologies. The prevalence of the mutations measured at baseline and post-treatment may provide information on response or resistance to therapy.

#### 4.5.11.6 Messenger RNA Expression Profiling

In cases where there is sufficient archival tissue to isolate RNA, gene expression will be performed using gene expression assays conducted on the NanoString platform or equivalent. Analysis may include, but is not limited to, a panel of genes important for intrinsic subtyping, breast cancer biology and PI3K signaling. The goal will be to generate a database of expression status to examine whether there are gene expression patterns that are associated with clinical response to GDC-0032.

#### 4.5.11.7 Next Generation Sequencing

In cases where there is sufficient material to isolate DNA, NGS will be performed using NGS platforms, such as Illumina or equivalent. The goal will be to determine whether the percentage of genetic mutations are associated with clinical response to GDC-0032.

#### 4.5.11.8 Copy Number Analysis

The level of copy number alterations in cancer-related genes may be determined using DNA-based technologies, either cytogenetically using chromosomal in situ hybridization (ISH), using next-generation sequencing platforms or by RT-PCR-based or equivalent technologies. For cytogenetic assays, detection may be either fluorescence-based (fluorescence in situ hybridization assay) or chromogenic-based (chromogenic in situ hybridization). Increased copy number of PI3K pathways activating genes may provide information on response or resistance to therapy.

#### 4.5.11.9 Plasma Biomarker Analyses

Assays to assess the expression of soluble, systemic cytokines, and chemokines from the plasma of patients will be carried out using appropriate methodologies, such as enzyme-linked immunosorbent assay (ELISA)-based or mass spectrometry-based or equivalent technologies.

#### 4.5.11.10 Plasma Pharmacokinetic Samples

Plasma GDC-0032 and letrozole samples will be analyzed using a validated liquid chromatography tandem mass spectrometry.

After the plasma samples are analyzed, any remaining samples may be used for exploratory metabolite profiling and identification, ex vivo protein binding, and PK, or pharmacodynamic assay development purposes.

#### 4.5.11.11 Pharmacogenetic Polymorphism Assay

If approved by the local regulatory authority, gene mutations will be assayed using multiplex PCR, allele-specific PCR, direct sequencing, or other acceptable methods. Results may be correlated to population PK parameters or other clinical measures in order to better understand the impact of genetic variants on drug metabolism, exposure, adverse events, and/or response.

A sample will also be utilized as a source of normal DNA to determine whether sequence variants in the *PIK3CA* gene and in other relevant oncogenes in the tumor DNA are somatic mutations or single nucleotide polymorphisms.

#### 4.5.11.12 Electrocardiograms

Triplicate ECG recordings will be obtained at each specified timepoint (see the schedule of assessments in Appendix 1).

#### 4.5.11.13 *DLCO Testing*

*A diffusion capacity of the lung for carbon monoxide (DLCO) test will be required at baseline and at the end of study-drug treatment (prior to surgery) for all patients. The DLCO test should be repeated if there is clinical suspicion of pneumonitis. Further guidance regarding DLCO testing is contained in Appendix 7 and in the management guidelines for pneumonitis (Section 5.1.1.2).*

#### 4.5.11.14 *Osteoporosis Assessment and Monitoring*

*Treatment with aromatase inhibitors results in bone loss due to estrogen deficiency. For patients who have a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis, a bone mineral density assessment will be required at baseline prior to initiating study treatment. Baseline bone mineral density will be measured via dual-energy X-ray absorptiometry (DXA). DXA measurement of both the hip and lumbar spine is suggested. When either the hip or lumbar spine is not a valid skeletal site for a bone mineral density measurement, then the 33% (one-third) radius should be measured. In some patients, measurement of the hip alone could be sufficient.*

*Appropriate monitoring in these patients will occur per institutional guidelines. Assessment for fractures is already included as part of the scheduled physical examinations. Determination of patients who are at increased risk for osteoporosis will be per institutional guidelines. Clinical risk factors for fracture include advancing age, previous fracture, glucocorticoid therapy, parental history of hip fracture, low body weight, current cigarette smoking, excessive alcohol consumption, rheumatoid arthritis, and secondary osteoporosis (e.g., hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease) (Kanis et al., 2005).*

### 4.5.12 Patient-Reported Outcomes

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of GDC-0032. The PRO questionnaires, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

The EORTC QLQ-C30 and the Modified Breast Cancer module QLQ-BR23 questionnaires will be used to assess HRQoL, including side-effects of systemic therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems) and patient functioning during the neoadjuvant period (refer to schedule of assessments in Appendix 1 for a detailed description of timepoints) and post-surgery follow-up.

The EORTC QLQ-C30 is a widely used HRQoL measure in oncology trials with excellent psychometric properties demonstrating both reliability and validity. The measure consists of “five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale” with a recall period of “the past week” (Aaronson et al. 1993). Scale scores can be obtained for each of the multi-item scales, global health status/QoL scale, and six single items by using a liner transformation for standardization of the calculated raw score.

The EORTC QLQ-BR23 breast cancer module was first validated for use in 1995, uses a recall period of “the past week,” and is intended for use across multiple treatment modalities (i.e., surgery, chemotherapy, radiotherapy, and hormonal treatment). As this trial will include patients in the neo-adjuvant setting, the last seven items of the original BR23 questionnaire, items numbered 47 – 53 that deal with symptoms and side effects not relevant to the population under study, will be removed. These seven items addressed symptoms experienced by metastatic breast cancer patients and those undergoing radiation. Therefore, in consultation with the EORTC, these items were deleted, as the validity of the measure would not be compromised by their removal. In addition, as “oral mucositis” and “skin problems” are key symptoms of this therapy not assessed by currently available tools, validated items from the EORTC item bank were added to assess the presence and bothersomeness of oral mucositis (2 items: sore

mouth/tongue, difficulty swallowing) and skin problems (2 items). Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results. Scale scores can be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score.

The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. Patients must complete these instruments in the clinic (cannot be taken home) prior to any healthcare provider interactions (i.e., prior to administration of study drug and prior to any other study assessment) to ensure that the validity of the instruments are not compromised and to ensure that data quality meet regulatory requirements.

Refer to Appendix 4 for the EORTC QLQ-C30 and the modified QLQ-BR23.

### 4.5.13 Samples for Clinical Repository

All residual samples (or leftover biologic samples after protocol-defined studies are completed) obtained during the study (FFPE, fresh-frozen, plasma, etc.) will be stored in an academic central repository. The specimens in the study repository will be made available for future biomarker research towards further understanding of treatment with GDC-0032, of breast cancer, related diseases, and adverse events, and for the development of potential, associated diagnostic assays. The implementation of study repository specimens is governed by the Study Steering Committee, with guidance from a dedicated Translational Research Committee to ensure the appropriate use of the study specimens.

All biomarker specimens will be retained for new research related to this study and/or disease in accordance with the recommendations and approval of the Study Steering Committee. Samples will be only destroyed if required by local laws relating to the collection, storage, and destruction of biological specimens.

Specimens will be stored up to 15 years or until they are exhausted. The storage period will be in accordance with the institutional review board/ethics committee (IRB/EC)-approved ICF and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

#### 4.5.13.1 Confidentiality

Patient medical information associated with biologic specimens is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for

use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from biologic specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using biologic specimens will be available in accordance with the effective Translational Reseach Committee policy on study data publication.

## 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

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.

### 4.6.2 Study Treatment Discontinuation

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

- Pregnancy
- Disease progression
- Unacceptable toxicity

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 Conditions for Terminating the Study

Both the Sponsor and the investigator reserve the right to terminate their participation in the study under the circumstances agreed upon in the site agreement. Should this be necessary, both parties will arrange the procedures on an individual basis after review and consultation. In terminating the study, the Sponsor and investigator will assure that adequate consideration is given to the protection of the patients' interest.

# 5. ASSESSMENT OF SAFETY

## 5.1 SAFETY PLAN

GDC-0032 is not approved and is currently in early clinical development. Thus, the entire safety profile is not known at this time. Human experience is currently limited. The following information is based on results from ongoing clinical studies. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events, and laboratory abnormalities (see Section 5.3.5.3), defined and graded according to NCI CTCAE v4.0. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistry and blood counts. All serious adverse events and non-serious adverse events of special interest will be reported in an expedited fashion, via fax to Austrian Breast and Colorectal Cancer Study Group (ABCSG) safety department and also captured in the electronic data capture (EDC) system. In addition, the Sponsor and the investigators will review and evaluate observed adverse events on a regular basis.

All adverse events will be recorded during the trial and for 30 days after the last dose of study treatment or until the end of study visit, whichever occurs later. Patients who have an ongoing study treatment-related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

All adverse events should be attributed by the investigator to study drug or to another clearly identified etiology by the investigator (see Table 10).

Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections.

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

### 5.1.1 Management of Specific Adverse Events of GDC-0032

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

Due to the approximately 40-hour half-life for GDC-0032, investigators should consider holding GDC-0032 for certain Grade 2 toxicities until the adverse event resolves to Grade ≤ 1 as discussed below (e.g., stomatitis/mucositis, colitis, rash, diarrhea, pneumonitis). Certain toxicities can occur within 1–2 weeks of holding or discontinuing

GDC-0032 drug (e.g., pneumonitis, colitis, rash). In these cases, the adverse event eventually resolves. Investigators should follow management guidelines and dose modifications for toxicities as described below, including administration of topical or systemic corticosteroids as appropriate.

**Table 1 Overall Dose Modification Guideline for GDC – 0032-Related Adverse Events**

| | GDC-0032 |
|---|---|
| Starting dose | 6 mg at 5 days on / 2 days off |
| First reduction | 3 mg at 5 days on / 2 days off |
| Second reduction | 3 mg at 3 days on / 4 days off [a] |

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

#### 5.1.1.1 Management of Hyperglycemia

Hyperglycemia has been observed in patients who received GDC-0032 in the single-agent Phase I study.

Patients with diabetes requiring daily anti-hyperglycemic medication or who have a fasting blood glucose level $>$125 mg/dL will be excluded from the study. $HbA_{1c}$ and fasting glucose levels will be monitored at baseline, and additional monitoring of fasting glucose levels during the study will be implemented, as outlined in the schedule of assessments. Patients should be instructed to report symptoms associated with hyperglycemia such as thirst, frequent urination, and blurred vision.

Metformin is the first antihyperglycemic medication of choice because of the lower risk of hypoglycemia with this agent. Because metformin in some patients may also cause diarrhea and not be well tolerated, other antihyperglycemic medications such as sulfonylureas (e.g., glimepiride, glipizide) can be used. Extra caution should be used with other drugs such as sulfonylureas because of the increased risk for hypoglycemia with these agents. Consultation with an endocrinologist can be helpful in managing hyperglycemia.

Specific dose modification and management guidelines for hyperglycemia are provided in Table 2.

**Table 2 Dose Modification and Management Guidelines for Hyperglycemia (Based on Fasting Blood Glucose)**

| Grade | Dose Modification and Management Guidelines for Hyperglycemia (based on fasting blood glucose) |
|---|---|
| Grade 2 | Initiation of an anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring will be implemented.<br>Dosing with GDC-0032 may either be held or continued per investigator evaluation. |
| Grade 3 (asymptomatic) | GDC-0032 dosing will be suspended and the patient will be managed as per standard of care, including implementation of additional glucose monitoring and initiation of, or an increase in, the dose of an anti-hyperglycemic therapy (e.g., metformin).<br>If the hyperglycemic event does not improve to Grade ≤ 1 within 28 days, GDC-0032 will be permanently discontinued.<br>If the hyperglycemic event improves to Grade ≤ 1 within 28 days, GDC-0032 dosing may resume at one dose level lower, with approval by the Medical Monitor. |
| Grade 3 (symptomatic) [a], Grade 3 (requiring hospitalization), or Grade 4 | GDC-0032 dosing will be suspended, and the patient will be managed as per standard of care, including implementation of additional glucose monitoring and initiation of, or an increase in, the dose of anti-hyperglycemic therapy.<br>If the hyperglycemic event does not improve to Grade ≤ 1 within 28 days, GDC-0032 will be permanently discontinued.<br>If the hyperglycemic event improves to Grade ≤ 1 within 28 days, GDC-0032 dosing may resume at one dose level lower, with approval by the Medical Monitor. |

[a] For example, blurred vision, frequent urination, excessive thirst.

#### 5.1.1.2 Management of Pneumonitis

Patients who require any daily supplemental oxygen are not eligible for the study. *Patients who have DLCO values <60% will be excluded from the study.* Patients will be assessed for pulmonary signs and symptoms throughout the study. *The DLCO test should be repeated if there is clinical suspicion of pneumonitis. The DLCO test will also be repeated presurgery after completion of study treatment.* Management guidelines for patients with possible pneumonitis are listed in Table 3.

**Table 3 Dose Modification and Management Guidelines for Pneumonitis**

| Grade | Intervention | Investigations | GDC-0032 [a] Dose Adjustment |
|---|---|---|---|
| 1 | No specific therapy required. | CT scan. Consider $DLCO$. [b] Repeat CT scan every 8 weeks until return to baseline. | No change. |
| 2 | Symptomatic only. Prescribe corticosteroids if cough is troublesome. | CT scan. Repeat CT scan $and\ DLCO$ every 4 weeks until return to baseline. Consider bronchoscopy. | Reduce dose until improvement to Grade ≤ 1; consider interruption if symptoms are troublesome.<br>Interrupt treatment as long as corticosteroids are being given.<br>Restart GDC-0032 at the same dose if clinical benefit evident. Consider restarting at reduced dose if recurrent event or per discussion with Medical Monitor.<br>Discontinue treatment if recovery to Grade ≤ 1 is not evident within 28 days. |
| 3 | Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated. | CT scan. Repeat CT scan $and\ DLCO$ every 4 weeks until return to baseline. Bronchoscopy is recommended. | Interrupt treatment until improvement to Grade ≤ 1.<br>Restart therapy within 28 days at a reduced dose if clinical benefit is evident.<br>Interrupt treatment as long as corticosteroids are being given. |
| 4 | Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated. | CT scan. Repeat CT scan $and\ DLCO$ every 4 weeks until return to baseline. Bronchoscopy is recommended. | Discontinue treatment. |

Table modified from White et al. 2010.

CT = computed tomography; $DLCO = diffusion\ capacity\ of\ the\ lung\ for\ carbon\ monoxide$.

[a] Dose reductions per Section 5.1.1.

[b] $DLCO$ may be useful to monitor the effect of interventions such as dose reduction/discontinuation and corticosteroids, in conjunction with imaging (White et al. 2010).

#### 5.1.1.3 Management of Rash

Rash and other dermatological events should be closely monitored, and patients with severe rash should be monitored for associated signs and symptoms such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. For severe rash, dosing of GDC-0032 should be interrupted, and patients should be treated with supportive therapy per standard of care. Use of antihistamines, as well as topical or systemic corticosteroids, may be considered (see Table 4).

**Table 4 GDC-0032 Dose Modification and Management Guidelines for Rash**

| Grade of Rash | GDC-0032 |
|---|---|
| Grade 1 | Continue dosing at current dose and monitor for change in severity.<br>Consider prescribing topical corticosteroids [a] |
| Grade 2 | Consider holding GDC-0032 or reducing to the next lower dose if rash is troublesome.<br>Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]). |
| Grade 3 or 4 | Hold GDC-0032 until Grade ≤ 1.<br>Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]).<br>Consider dermatological consultation.<br>Consider obtaining photographs of rash if permitted by local regulations.<br>After rash improves to Grade ≤ 1, restart GDC-0032 at the next lower dose upon discussion with Medical Monitor, or permanently discontinue. |

AE = adverse event.

AE grading is based on NCI CTCAE, Version 4.0.

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

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

#### 5.1.1.4 Management of Gastrointestinal Toxicity

##### 5.1.1.4.1 Management of Diarrhea

Patients should be closely monitored for gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain, stomatitis, and changes in stool, including checking for blood in stool if clinically indicated). Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. Gastrointestinal symptoms should be managed per protocol guidelines and institutional standard of care. For example, prompt management of diarrhea with antidiarrheal medications should be implemented. Because of the approximately 40-hour half-life of GDC-0032, investigators should hold GDC-0032 for Grade ≥ 2 diarrhea until it improves to Grade ≤ 1.

Specific dose modification and management guidelines for diarrhea are provided in Table 5.

## Table 5 GDC-0032 Dose Modification and Management Guidelines for Diarrhea

| Grade of Diarrhea | Dose Modification and Management Guidelines |
|---|---|
| Grade 1 | • Manage per institutional standard of care that includes antidiarrheals. [a] |
| Grade 2 | • Hold GDC-0032 and manage per institutional standard of care until Grade $\leq$ 1. These include antidiarrheals. [a]<br>• For persistent Grade 2 non-infectious diarrhea despite treatment with antidiarrheals, additional coadministration of corticosteroids (e.g., budesonide 9 mg PO QD) are recommended. [b] Non-infectious diarrhea can be diagnosed by stool culture.<br>• For persistent Grade 2 diarrhea lasting longer than 1 week with an adequate trial of anti-diarrheal medications, or for recurrent Grade 2 diarrhea, restarting at the next lower dose level should be strongly considered after diarrhea improves to Grade $\leq$ 1.<br>• If Grade 2 diarrhea is persistent despite treatment with SOC, consider work-up for colitis (e.g., performing abdominal/pelvis CT and/or endoscopy, and stool culture as appropriate). |
| Grade 3 or 4 | • Hold GDC-0032 and manage per institutional standard of care until Grade $\leq$1. These include antidiarrheals. [a]<br>• Consider work-up for colitis (e.g., performing abdominal/pelvis CT and/or endoscopy, and stool culture as appropriate).<br>• Restart GDC-0032 at the next lower dose level upon resolution to Grade$\leq$1.<br>• For persistent Grade 3$-$4 non-infectious diarrhea despite treatment with antidiarrheals, administration of systemic corticosteroids should be considered. [b]<br>• For Grade 3 diarrhea, may consider restarting at the same dose if event occurred because of lack of optimal medical management with antidiarrheal medications, after discussion with and approval by the medical monitor.<br>• For Grade 4 diarrhea, consider permanent discontinuation of GDC-0032. |

CT = computed tomography; PO = oral; QD = once daily; SOC = standard of care.

[a] Suggested antidiarrheals include the following: loperamide (initial: 4 mg, followed by 2 mg after each loose stool, up to 16 mg/day); diphenoxylate and atropine (Diphenoxylate 5 mg 4 times/day until control achieved [maximum: 20 mg/day], then reduce dose as needed; some patients may be controlled on doses of 5 mg/day; tincture of opium (6 mg of undiluted opium tincture [10 mg/mL]) 4 times daily.

[b] Examples of corticosteroid regimens include the following: For the steroid taper, suggested steroids include a methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg $\times$ 2 days, 40 mg $\times$ 2 days, 20 mg $\times$ 2 days, etc.). Can also consider budesonide 9 mg PO QD or prednisone 5 mg to 10 mg PO QD.

#### 5.1.1.4.2 Management of Colitis

Data as of October 2013 show an incidence rate for colitis of 6.2% (10/160) (1 at 16 mg; 8 at 9 mg; 1 at 6 mg + fulvestrant) with onset at approximately 100 days or longer after initiation of treatment with daily GDC-0032 dosing. Some patients have developed Grade 2 or Grade 3 diarrhea, which is non-responsive to anti-diarrheal medication. In some of these patients, a CT scan or colonoscopy has revealed colitis, which has resolved upon treatment with systemic corticosteroids.

For persistent Grade 2 diarrhea that does not resolve or for Grade $\geq$ 3 diarrhea, further evaluation should include colitis in the differential diagnosis with the appropriate work-up (e.g., abdominal/ pelvis CT scan, endoscopy with biopsy, stool cultures for cytomegalovirus, Clostridium difficile, and parasites). Grade $\geq$ 2 colitis should be managed by interruption of study treatment. In addition, discontinuation of nonsteroidal anti-inflammatory medications or any other medications known to exacerbate colitis symptoms should be considered. If noninfectious colitis is suspected, treatment with corticosteroids per institutional standard of care should be considered. It is suggested that prednisone (for oral administration) or solumedrol (for IV administration) are the corticosteroids of choice in the treatment of colitis. For severe symptoms, prednisone 60 mg or equivalent may be required to control initial symptoms, and the dose should be gradually tapered. Lower doses of prednisone, oral budesonide, or mesalamine (or other 5-aminosalicyclic acid derivatives) may be considered for less severe cases of colitis.

Specific dose modification and management guidelines for colitis are provided in Table 6.

**Table 6 GDC-0032 Dose Modification and Management Guidelines for Colitis**

| Grade of Colitis | Dose Modification and Management Guidelines |
|---|---|
| Grade 2 or Grade 3 (first event) | • Hold GDC-0032 and manage per institutional standard of care until Grade ≤ 1.<br>• Initiate corticosteroid therapy for noninfectious colitis. [a]<br>• Recommend discontinuation of any nonsteroidal anti-inflammatory medications or any other medications known to exacerbate colitis symptoms.<br>• Restart GDC-0032 at the next lower dose level upon resolution to Grade ≤ 1. In cases where risk/benefit is deemed favorable, may consider restarting at the same dose after discussion with and approval by the Medical Monitor. |
| Grade 3 (first recurrence) | • Hold GDC-0032.<br>• Initiate corticosteroid therapy for noninfectious colitis. [a]<br>• Permanently discontinue GDC-0032. In cases where risk/benefit is deemed favorable, may consider restarting at the next lower dose level upon resolution to Grade ≤ 1 after discussion with and approval by the Medical Monitor. |
| Grade 3 (second recurrence) or Grade 4 | • Permanently discontinue GDC-0032.<br>• Initiate corticosteroid therapy for noninfectious colitis. [a] |

[a] Examples of corticosteroid regimens include the following: For the steroid taper, suggested steroids include methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg × 2 days, 40 mg × 2 days, 20 mg × 2 days, etc.).

#### 5.1.1.4.3 Management of Stomatitis and Oral Mucositis

Aggressive mouth care for oral mucositis and stomatitis with mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) may also be helpful in managing symptoms, and it is recommended that these are implemented with early signs of dry mouth, Grade 1 mucositis, or Grade 1 stomatitis (see Table 7). Avoidance of spicy foods may also be helpful.

**Table 7 GDC-0032 Dose Delay and Modification Guidelines for Stomatitis and Oral Mucositis**

| Grade of Stomatitis/Mucositis | GDC-0032 |
|---|---|
| All grades | • Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics)<br>• Diet management (e.g., avoidance of spicy foods) |
| Grade 1 | • Monitor symptoms and initiate management (see above). Re-evaluate within 48 – 72 hours. |
| Grade 2 | • Hold GDC-0032 and manage until Grade ≤ 1.<br>• Restart GDC-0032 at the same dose.<br>• If Grade 2 stomatitis/oral mucositis recurs, hold GDC-0032 until Grade ≤ 1. Restart GDC-0032 at the next lower dose. |
| Grade 3 or 4 | • Hold GDC-0032 and manage until Grade ≤ 1. Restart GDC-0032 at the next lower dose.<br>• For Grade 3 event that was not adequately managed upon initial presentation, consider restarting at same dose upon discussion with Medical Monitor.<br>• For Grade 4 event, consider permanent discontinuation of GDC-0032. |

### 5.1.2 Management of Other Clinically Significant Adverse Events

See Table 8 for the dose modifications for other clinically significant adverse events.

**Table 8 GDC-0032 Dose Delay and Modification Guidelines for Other Clinically Significant Adverse Events**

| Grade | GDC-0032 |
|---|---|
| Grade 3: first event | • Hold GDC-0032 until Grade ≤ 1.<br>• Consider restarting at next lower dose. |
| Grade 3: recurrent<br>Grade 4: non-life-threatening | • Hold GDC-0032 until Grade ≤ 1.<br>• Restart at next lower dose. |
| Grade 4: life-threatening | • Permanently discontinue GDC-0032. |

### 5.1.3 General Guidance for Dose Modifications and Delays for Letrozole

The letrozole dose level cannot be modified. In general, the investigator can consider continuing letrozole if it is not thought to be letrozole-related.

All dose modifications should be based on the adverse event requiring the greatest modification and should be properly documented in the source documents.

### 5.1.4 Management of Increases in QT Interval

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

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

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

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

In rare circumstances, it may be acceptable to resume study drug, at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

### 5.1.5 Safety Monitoring for Letrozole

Letrozole is a nonsteroidal AI indicated for first line treatment of hormone receptor positive, locally advanced, or metastatic breast cancer in postmenopausal women. Letrozole is also indicated for adjuvant treatment in postmenopausal hormone-receptor positive patients and for the treatment of advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

The most frequently reported adverse events in a first line, breast cancer clinical trial with letrozole were bone pain, hot flushes, back pain, nausea, arthralgia, and dyspnea. Clinically significant adverse events also include bone effects (osteoporosis and bone fractures) and hypercholesterolemia. Discontinuations for adverse events other than progression of tumor occurred in 2% of patients on letrozole. Refer to the U.S. letrozole Package Insert or SmPC for additional information.

There are no expected significant overlapping toxicities between letrozole and GDC-0032. Routine safety monitoring and periodic laboratory tests for the letrozole and GDC-0032 combination will occur throughout the study.

## 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; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and 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 ABCSG)

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

- Fatal (i.e., the adverse event actually causes or leads to death)
- 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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 (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 ABCSG safety department 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 ABCSG)

Non-serious adverse events of special interest are required to be reported by the investigator to ABCSG safety department 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:

- Grade 4 hyperglycemia
- Grade $\geq$ 3 symptomatic hyperglycemia
- Grade $\geq$ 2 colitis or enterocolitis
- Grade $\geq$ 3 diarrhea
- Grade $\geq$ 3 rash
- Grade $\geq$ 2 pneumonitis

- 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 5.3.5.5)
- Suspected transmission of an infectious agent by the study drug

## 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 additionally reported to ABCSG safety department in case they fulfill the criteria for expedited reported in accordance with instructions provided in this section and in Section 5.4 –Section 5.6.

For each adverse event recorded on the Adverse Event CRF, 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

**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 until the end of study visit, whichever occurs later. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern deemed related to prior study drug treatment or study procedures (Section 5.6).

### 5.3.2 Eliciting Adverse Event Information

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

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

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

### 5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 4.0) will be used for assessing adverse event severity. Table 9 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 9 Adverse Event Severity Grading Scale**

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

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

Note: Based on the most recent version of NCI CTCAE (v 4.0), 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 one's self, 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 10):

- 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 (where 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 10 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 | Adverse events will be considered related, unless they fulfill the criteria as specified below.<br>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.

If known, a diagnosis 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.

#### 5.3.5.1 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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.

#### 5.3.5.2 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. The progression (increase and decrease) of an adverse event must be documented in the Adverse Event eCRF.

The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

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

#### 5.3.5.3 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:

- 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
- Clinically significant in the investigator's judgment

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 the 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

#### 5.3.5.4 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:

- 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
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

#### 5.3.5.5 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × 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 ABCSG safety department immediately (i.e., no more than 24 hours after learning of the event), either as serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

#### 5.3.5.6 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 ABCSG safety department (see Section 5.4.2). This includes death attributed to progression of breast cancer.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term “sudden death” should only be used 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 of 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.

#### 5.3.5.7 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 CRF.

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”).

#### 5.3.5.8 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:

- Perform an efficacy measurement for the study
- Hospitalization for respite care
- Planned hospitalization required by the protocol for breast cancer surgery
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
    - The patient has not suffered an adverse event
- Hospitalization due solely to progression of the underlying cancer
- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care
- Hospitalization for protocol mandated biopsies

#### 5.3.5.9 Adverse Events Associated with an Overdose

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 serious criteria, the event should be reported to the ABCSG safety department immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

#### 5.3.5.10 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO ABCSG

Certain events require immediate reporting to allow ABCSG safety department to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to ABCSG safety department 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 ABCSG safety department 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 ABCSG safety department 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

**U.S. Medical Monitor Contact Information**

Genentech's Medical Monitor Contact Information:

Medical Monitor: [redacted], M.D., Ph.D.

Telephone No.

Alternate Telephone No.: [redacted]

**Medical Monitor Contact Information for Sites outside the United States:**

Please refer to the country/region-specific phone numbers provided in the study binder.

### 5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the paper Serious Adverse Event reporting form and transmit to ABCSG safety department via fax. In addition the serious adverse event and non-serious adverse event of special interest information will be captured in the EDC system.

| | |
|---|---|
| Worldwide Sites: | ABCSG safety department |
| Fax No.: | +43 1 409 09 90 |

Relevant follow-up information should be submitted to ABCSG safety department as soon as it becomes available and/or upon request.

## 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 (SDV). For follow-up reports of serious adverse events and non-serious adverse events of special interest, investigators should record all follow up information immediately (i.e., within 24 hours) on the paper Serious Adverse Event reporting form and transmit to ABCSG safety department via fax. In addition the serious adverse event and non-serious adverse event of special interest follow-up information will be captured in the EDC system. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF and paper Serious Adverse Event form, if applicable.

All pregnancies reported during the study should be followed until pregnancy outcome, and they should be reported according to the instructions provided in Section 5.4.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor and/or ABCSG safety department 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

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should report these events directly to Genentech Safety Risk Management via telephone at 1-888-835-2555.

## 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:

- GDC-0032 Investigator's Brochure
- Local prescribing information for letrozole SmPC

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.

An IDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Primary and secondary efficacy analyses will include all patients who were included in the randomization. Final analysis will be performed after last patient, last visit (LPLV) and subsequent data cleaning, with patients allocated to the treatment arm associated by randomization.

Safety analyses will include all patients who were included in the randomization and received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

## 6.1 DETERMINATION OF SAMPLE SIZE

This study is designed for testing the effect of GDC-0032 on the two co-primary endpoints in all enrolled patients and in the *PIK3CA* MT patients and plans to enroll 330 patients in total. Assuming the *PIK3CA* mutation status will not be available (unknown) for approximately 10% of the patients and the prevalence of *PIK3CA* mutant is 40%, there will be approximately 120 patients in the *PIK3CA* MT cohort.

Given that the *PIK3CA* mutation status is not a stratification factor for randomization, there might be a possible imbalance between treatment arms within the *PIK3CA* MT cohort, which may reduce the statistical power in this cohort. To ensure the study provides sufficient statistical power even when the treatment assignment is imbalanced, the sample size was calculated based on a conservative scenario by assuming that the treatment assignment imbalance in *PIK3CA* MT is 40% vs. 60%. The sample size was calculated based on a chi²-test using continuity correction (Ury and Fleiss 1980).

To control an overall, two-sided, family-wise error rate under 20%, we use a two-sided significance level of 16% and 4% for the co-primary endpoints MRI ORR, and pCR, respectively.

Assuming 10% of the patients are unevaluable for the MRI ORR, approximately 300 enrolled patients and 108 patients in the *PIK3CA* MT cohort will be evaluable for analyses. This sample size allows us to detect an absolute percentage increase of 24% in MRI ORR rate in the GDC-0032 plus letrozole arm (64%) versus the letrozole-only arm (40%; Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at 80% power and 16% two-sided significance level. The minimal detectable difference for ORR is approximately 15%.

Assuming that all patients are evaluable for pCR (i.e., approximately 330 enrolled patients and 120 in the *PIK3CA* MT cohort), this sample size provides 80% power to detect an absolute percentage increase of 18% in pCR in the GDC-0032 plus letrozole arm (19%) versus the letrozole-only arm (1%, Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at the 4% two-sided significance level. The minimal detectable difference for pCR rate is approximately 13%.

If the prevalence of the *PIK3CA* mutation is lower than assumed, if there is more substantial treatment assignment imbalance in the *PIK3CA* MT cohort than assumed, or there is an increased number of unevaluable patients for the MRI ORR, the sample size may be increased to obtain the level of power at 80%, and the enrollment may be limited to patients with *PIK3CA* MT.

## 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 incidence of study treatment discontinuation for reasons other than disease progression will be tabulated.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables, stratification factors, and other baseline characteristics will be summarized by treatment arm.

## 6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include the ITT population; that is, all randomized patients will be included in the analyses, with patients grouped according to the treatment assigned at randomization.

### 6.4.1 Primary Efficacy Endpoint

The co-primary efficacy endpoints are (1) tumor ORR, assessed by modified RECIST criteria by breast MRI and (2) the rate of pCR in breast and axilla (total pCR) after completion of study drug.

The tumor ORR will be calculated by treatment arm in all enrolled population and in *PIK3CA* MT population. Within each population, the ORR for the two treatment arms will be compared at a two-sided alpha of 16% using a Cochran Mantel-Haenszel test, stratified by tumor size and nodal status. The pCR rate will also be calculated and compared at a two-sided alpha of 4% based on the same analytical approach as ORR. The two alpha values account for a family-wise type I error rate of 20%. Patients with early study termination and hence missing efficacy outcome will be considered as non-responders.

### 6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are as follows:

- Tumor ORR after completion of study treatment, assessed by modified RECIST criteria by breast MRI in *PIK3CA* WT patients.
- Rate of pCR in breast and axilla (total pCR) after completion of study drug in *PIK3CA* WT patients.
- These endpoint measures will be summarized by treatment arm and will be analyzed analogue to the primary efficacy endpoint.
- The following secondary efficacy endpoints will be performed in all enrolled patients and separated by *PIK3CA* mutation status:
- ORR by clinical breast examination, mammography, and breast ultrasound
- Ki67 values at baseline, Week 3, and surgery (centrally assessed)
- Change in Ki67 from baseline to Week 3; baseline to surgery, and Week 3 to surgery (centrally assessed)
- PEPI score (centrally assessed)
- Change in enhancing tumor volume from baseline to surgery as measured by breast MRI

- Evaluation of different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR)

These endpoint measures will be summarized by treatment arm and will be compared between the two treatment arms within each population based on appropriate statistical analyses: ORR will be compared using a Cochrane Mantel-Haenszel test, stratified by tumor size and nodal status; PEPI, Ki67, and tumor volume change will be compared by regression analyses, adjusted for tumor size and nodal status. All secondary endpoints will be tested at a two-sided type I error of 5%.

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

## 6.5 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, and letrozole and GDC-0032 exposure.

Verbatim descriptions of adverse events will be mapped to thesaurus terms. Adverse event data will be listed by study site, treatment arm, patient number, and study day, severity, relationship to study drug, outcome, and action taken with the study treatments. Events occurring on or after treatment on Day 1 of Week 1 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 and vital sign (heart rate, blood pressure, and temperature) data will be displayed by time, with NCI CTCAE v4.0 Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized in tables by NCI CTCAE v4.0 grade.

## 6.6 PHARMACODYNAMIC ANALYSES

Ki67 biomarker analyses will include patients with at least one predose and one postdose biomarker assessment, with patients grouped according to the treatment actually received.

## 6.7 PHARMACOKINETIC ANALYSES

Individual $C_{max}$ and trough plasma concentrations ($C_{min}$) of GDC-0032 and letrozole from all patients enrolled will be reported. Mean of trough plasma concentrations of GDC-0032 and letrozole will be tabulated. The population pharmacokinetics of letrozole and GDC-0032 in this study will be compared with historical single-agent pharmacokinetics to assess the potential DDI between GDC-0032 and letrozole in this population.

Additional PK analyses on metabolites of GDC-0032, letrozole, and/or other concomitant medications may be conducted as appropriate.

## 6.8 PATIENT-REPORTED OUTCOME ANALYSES

Patient-reported outcomes of breast cancer symptoms, patient functioning, and HRQoL will be assessed by the EORTC QLQ-C30 and the modified Breast Cancer module (QLQ-BR23)

Summary statistics (mean, standard deviation, median and range) of linear transformed scores will be reported for all the items and subscales of the EORTC QLQ-C30 questionnaire, and the modified QLQ-BR23 according to the EORTC scoring manual guidelines for each assessment time point. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) of items and subscales over time will be provided for each treatment arm from the baseline assessment.

Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results.

Completion and compliance rates will be summarized at each timepoint by treatment arm with reasons for missing data. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses. The number and proportion of patients who improved, worsened, or remained stable for all of the symptom and functional domains, global QoL, and single items of the EORTC QLQ-C30 and QLQ-BR23 will be summarized.

## 6.9 EXPLORATORY ANALYSES

Additional details on analyses will be specified in the SAP.

## 6.10 INTERIM ANALYSES

The IDMC will conduct interim analyses to review the unblinded safety data after the first 20 patients have either 1) finished the 30-day, follow-up visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery). All available information of all enrolled patients with all available assessments at the respective timepoint will be included in the interim analyses. In addition, the IDMC or the Medical Monitor may request additional ad hoc meetings of the IDMC at any time during the study to review safety data.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

ABCSG will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, ABCSG and/or all involved clinical research associates (CRAs) will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

ABCSG will produce a Data Management Plan that describes the quality checking to be performed on the data. The Sponsor will perform oversight of the data management of this study, including review of the ABCSG's data management plan and corresponding specifications. Data will be transferred electronically from ABCSG to the Sponsor at the end of the study and whenever otherwise contractually agreed, and the Sponsor's standard procedures will be used 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 at ABCSG and records retention for the study data will be consistent with the ABCSG's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff. Original PRO questionnaires will be kept in the patient's medical record as source documentation.

## 7.2 DATA(BASE) MANAGEMENT

ABCSG Clinical Data Management will check all e-forms for plausibility and consistency by automatic edit checks and manual data review according to study-specific data management plan (DMP). If necessary, web-based data queries (data clarification requests [DCRs]) will be generated and subsequently visible for the investigators, dedicated site staff, responsible CRAs, and responsible ABCSG staff. For those eCRFs which pass all verification procedures and are regarded as correct and complete, they will be frozen subsequently by ABCSG clinical data management. Consequently, no further data entries or changes on frozen eCRFs are possible. The status of frozen eCRFs is flagged by the specific icon.

Clinical Data Management ensures that the database is corrected for the following eCRF issues without immediate notification to site staff (self-evident corrections). Notification of site staff is provided via a specific report after final data cleaning procedures and before final data confirmation by the investigator or a designee:

- misspellings/typing errors that do not change the meaning of the word
- location of data recorded at an incorrect variable field or eForm (e.g., moving lab data from general comments to the appropriate lab table)

- standard time to 24-hour clock
- correction of date format, if required (dd/mm/yyyy)
- if equivalent units of terms are recorded instead of the acceptable ABCSG standard
- data changes due to plausibility checks and eCRF content (e.g., combination of several variables and/or eCRFs)

All data management workflows are described in detail in the relevant SOPs and working instructions of ABCSG.

## 7.3 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using the Clinical Data Management System "MACRO," a web-interface DATAPORT. Sites will receive training by the responsible CRAs and have access to a manual for appropriate eCRF completion (web data entry).

All eCRFs should be completed by designated, trained site staff in a timely manner, usually within 2 weeks after the patient visit. Electronic CRFs should be reviewed and respective data confirmation eCRF should be electronically signed and dated by the investigator or a designee at the end of the study.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a storage medium (compact disc [CD], digital video disk [DVD] etc.) that must be kept with the study records. Acknowledgement of receipt of the storage medium is required.

## 7.4 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

### 7.5 USE OF COMPUTERIZED SYSTEMS

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

### 7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data (if applicable), ICFs, 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 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP 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/European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

## 8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs) 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 ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved consent forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. 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 separate, specific 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 provide a separate signature.

**The ICFs must be signed and dated by the patient or the patient's legally authorized representative before participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.** The eCRF contains a section to document whether the patient has signed the ICF or not.

The ICFs 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.

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the patients are

completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs 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 ICF 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.

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the sponsor, the affiliated groups, or contract research organizations (CROs) according to the applicable local laws and regulations, if applicable 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 Sponsor, affiliated groups, or CROs are 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 local IRB/EC. The Sponsor, affiliated groups, or CROs 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 local health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 8.4 DATA PRIVACY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique 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 only be disclosed to third parties as permitted by the ICF (or separate authorization for use and

disclosure of personal health information) signed by the patient, unless permitted or required by local 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, provided the patient has given consent.

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. The patient will have to consent to such access by signing the informed consent form.

## 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (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, ICFs, and documentation of IRB/EC and governmental (health authorities) approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

## 9.2 ON SITE QUALITY CONTROL (MONITORING)

During the study, CRAs will visit their respective sites on a regular basis as outlined in the study specific monitoring plan (MP) and all other relevant specifications, in order to guarantee adherence to the protocol and to the principles of GCP and to check for the progress of enrolment, adequate storage conditions of IMP and adequate drug dispensing and accounting records.

CRAs will review documented data in the eCRFs for completeness and accuracy according to the study-specific MP, subsequently flag all reviewed pages with a specific mark ("SDV done") within the EDC system "MACRO," web-interface DATAPORT, developed by [redacted]. The CRAs will raise data queries ("DCRs") in cases of missing source data or incorrect data entries. Immediately after electronic issue of the queries, they become visible to the investigator, the clinical data managers, and the ABCSG clinical safety officers ("raised DCRs"). CRAs and/or clinical data managers

and/or ABCSG clinical safety officers will follow up with trial site personnel until final data query resolution.

## 9.3 PROTOCOL DEVIATIONS

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

## 9.4 SITE INSPECTIONS

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

## 9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech and will be managed by Genentech in collaboration with the Breast International Group (BIG), ABCSG, and the Spanish Breast Cancer Research Group (SOLTI). Genentech in collaboration with BIG, ABCSG, and SOLTI will provide clinical operations management, data management, and medical monitoring. Approximately 110 U.S. and international sites will participate to enroll approximately 330 patients.

An IDMC will be in place throughout the study and will provide oversight of safety and efficacy analyses (see Section 3.1.2).

After written informed consent has been obtained, the study site will obtain the patient's screening number from the IxRS system. Once eligibility has been established, the patient will be enrolled, and the study site will obtain the patient's identification number from the IxRS. Once results of the tissue analysis are made available, the patient will be randomized, and the site will obtain the blinded treatment assignment from the IxRS. The IxRS will manage GDC-0032/placebo drug inventory at all sites and letrozole drug inventory at all study sites outside the United States. IxRS will be required to randomize patients, to monitor enrollment and patient status, and to manage study treatment requests and shipments.

Patient data will be recorded via an electronic data capture (EDC) system from [redacted], United Kingdom), which will be managed by ABCSG using eCRFs (see Section 7.2).

Central laboratories, including Genentech and Genentech collaborators, will be used for *PIK3CA* mutation detection, Ki67, and PTEN status and/or will provide kits for PK, pharmacogenomic, tissue, whole blood, and plasma sample analyses to be conducted at central laboratories, Genentech, or Genentech collaborators.

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

## 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

| Study procedures | Screening | Treatment Phase | | | | | | Surgery [a,f] | Post Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | W9 | W13 | W16 (Presurgical Visit) | W17 – W18 (Surgery) | 4 Weeks (+1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (±2) | 29 (±2) | 57 (±2) | 85 (±2) | 106 – 112 | 113 – 126 | |
| Informed consent [a] | x | | | | | | | | |
| Medical history and demographic data [b] | x | | | | | | | | |
| Physical examination [c] | x | | | x | x | x | x | | x |
| Clinical breast and regional lymph node examination | x | x | | x | x | x | x | | |
| Vital signs [d] | x | x | x | x | x | x | x | | x |
| ECOG Performance Status | x | x | x | x | x | x | x | | x |
| 12-Lead ECG [e] | x | | x | | | | | | |
| Mammography | x | | | | | | x | | |
| Breast ultrasound and axillary lymph node status [f] | x | | | | x | | x | | |
| Breast MRI [g] | x | | | | | | x | | |
| Collection of tumor samples [h] | x | | x | | | | | x | |
| Confirmation of receipt of adequate tissue for *PIK3CA* assessment | x | | | | | | | | |
| CBC with differential and platelet count [i] | x | x | | x | x | x | x | | x |
| Fasting serum chemistry [j] | x | x | | x | x | x | x | | x |

# Appendix 1
# Schedule of Assessments (cont.)

| Study procedures | Screening | Treatment Phase | | | | | | Surgery [a,f] | Post Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | W9 | W13 | W16 (Presurgical Visit) | W17 – W18 (Surgery) | 4 Weeks (+1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | 57 (±2) | 85 (±2) | 106 – 112 | 113 – 126 | |
| Glycosylated hemoglobin ($Hb_{A1c}$) | x | | | | | | | | |
| Fasting insulin and glucose [k] | x | x | | x | x | x | x | | x |
| Fasting lipid profile and amylase [l] | x | | | x | | x | x | | x |
| Coagulation (INR and aPTT) | x | | | x | x | x | x | | x |
| Urinalysis (laboratory) [m] | x | | | x | x | | x | | x |
| *DLCO* [n] | *x* | | | | | | *x* | | |
| *Bone mineral density test* [o] | *x* | | | | | | | | |
| Blood sample for plasma protein biomarkers [p] | | x | | | x | | x | | |
| Blood sample for ctDNA [q] | | x | | | x | | x | | |
| Blood sample for NGS [r] | | x | | | | | | | |
| Pharmacogenomic sample [s] | | x | | | | | | | |
| Concomitant medication [t] | x | x | x | x | x | x | x | | x |
| Adverse events | x | x | x | x | x | x | x | | x |
| Inclusion/exclusion criteria [u] | x | | | | | | | | |
| Visit with breast surgeon (may occur from Week 13) | | | | | | x | | | |
| Surgery [v] | | | | | | | | x | |
| Randomization | x | | | | | | | | |
| Letrozole accountability/dispensation | | x | x | x | x | x | x | | |

# Appendix 1
# Schedule of Assessments (cont.)

| Study procedures | Screening | Treatment Phase | | | | | | Surgery [a,f] | Post Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | W9 | W13 | W16 (Presurgical Visit) | W17 – W18 (Surgery) | 4 Weeks (+1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | 57 (±2) | 85 (±2) | 106 – 112 | 113 – 126 | |
| GDC-0032/placebo accountability/ dispensation | | x | x | x | x | x | x | | |
| Patient-reported outcomes [w] | | x | | x | x | x | x | | x |
| Pharmacokinetic sample (see Appendix 2) | | x | x | | x | | | | |

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; *DLCO = diffusion capacity of the lung for carbon monoxide;* ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; MRI = magnetic resonance imaging; NGS = next-generation sequencing.

Note: All assessments should be performed before dosing, unless otherwise stated. Some assessments may be performed outside the window indicated to accommodate holidays, unforeseen scheduling issues, or ongoing safety issues with the trial and the patient, after approval by the Medical Monitor.

[a] Perform within 28 days prior to Day 1 of Cycle 1. Signed informed consent must be provided prior to any study-specific evaluations. Assessments performed as standard of care within the timeframe may be used.

[b] Medical history includes clinically significant diseases that are currently active or that were active within the last 5 years, surgeries, cancer history (including date of diagnosis, primary tumor histology, grade, staging, prior cancer therapies, and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse. Demographic data include age, sex, and self-reported race/ethnicity.

[c] A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems as well as weight (in kilograms) and height (in centimeters; height is measured at the screening visit only). Perform symptom-directed physical examination after baseline assessment.

[d] Vital signs include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position and temperature. Oxygen saturation is obtained by pulse oximetry after the patient has been in a seated position for ≥ 5 minutes. Obtain vital signs predose.

[e] Triplicate ECG recordings will be obtained at each specified timepoint. A window of ± 30 minutes is acceptable for all timepoints. Submit all ECGs to the diagnostic facility for central review.

[f] Baseline evaluation of axillary lymph nodes assessed with ultrasound.

[g] MRI evaluation is optional at Week 9. MRI is mandatory at Week 9 in the event that disease progression is suspected, or if the primary lesion is not evaluable by ultrasound at baseline. Send all scans to the central reading facility for evaluation.

# Appendix 1
# Schedule of Assessments (cont.)

[h] Two formalin-fixed, paraffin-embedded core needle biopsies and one freshly frozen OCT core needle biopsy are required prior to initiation of treatment (pretreatment) and also on Day 15. A formalin-fixed, paraffin-embedded tumor block from a surgical resection is required at surgery (Weeks 17 – 18).

[i] Complete blood count includes red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[j] Fasting (≥10-hour fast) serum chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[k] Glucose levels may be obtained by fingerstick. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[l] Fasting lipid profile includes total cholesterol, HDL, LDL, triglycerides, amylase, and lipase. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[m] Includes specific gravity, pH, glucose, protein, ketones, and blood. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[n] *DLCO is obtained at screening and prior to surgery. The DLCO test should be repeated if there is clinical suspicion of pneumonitis. DLCO calculations are described in Appendix 7. The hemoglobin value used for correcting DLCO should represent the patient's actual hemoglobin level and should be obtained within 7 days of the DLCO test.*

[o] *Baseline bone mineral density will be measured via dual-energy X-ray absorptiometry (DXA) and will need to be obtained in women with a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis. DXA measurement of both the hip and lumbar spine is suggested. When either the hip or lumbar spine is not a valid skeletal site for BMD measurement, then the 33% (one-third) radius should be measured. In some patients, measurement of the hip alone could be sufficient.*

[p] Pretreatment sample for plasma protein biomarkers should be obtained prior to dosing. Refer to laboratory manual for more information.

[q] Pretreatment sample for ctDNA may be obtained on Day 1 prior to dosing. This sample will also be collected prior to dosing at Week 9 and at Week 16. Refer to laboratory manual for more information.

[r] Blood for NGS will be collected if allowed by local regulatory authorities and may be obtained prior to dosing on Week 1.

[s] Blood for pharmacogenomics will be collected if allowed by local regulatory authorities and may be obtained prior to dosing on Week 1.

[t] Record all medications used by the patient within 15 days before screening (including prescription, over-the-counter, herbal remedies, and supplements).

[u] All of the study's inclusion criteria and none of the exclusion criteria should be met prior to study entry.

[v] Surgery will take place after at least 16 weeks of combination treatment (i.e., from Week 17 to Week 18), and generally no more than 2 days after the last dose of study medication.

[w] The PRO questionnaires (EORTC QLQ-C30, modified QLQ-BR23) will be completed by the patients at the investigational site. All PRO questionnaires must be administered prior to any other study assessment(s) and prior to administration of study drug.

# Appendix 2
# Schedule of Pharmacokinetic Assessments

| Visit | Timepoint | PK Assessments |
|---|---|---|
| Day 1 | 3 hours post (±60 min) letrozole and GDC-0032/placebo administration | Letrozole PK |
| | | GDC-0032 PK |
| Day 15 (+2 days) | 0 – 4 hours prior to letrozole and GDC-0032/placebo administration | Letrozole PK |
| | | GDC-0032 PK |
| | 3 hours (±60 min) post letrozole and GDC-0032/placebo administration<br>ECG before PK | Letrozole PK |
| | | GDC-0032 PK |
| Day 57 (+/– 2 days) | 3 hours post (±60 min) letrozole and GDC-0032/placebo administration | Letrozole PK<br>GDC-0032 PK |

ECG = electrocardiogram; min = minutes; PK = pharmacokinetics.

Record exact time of dose administration and sample collection.

# 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 therapy in early breast cancer. Ultrasound, mammography, and clinical exam are all

[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.

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

### 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

## 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.

**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.

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

## 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
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures

## EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): _____

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

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

Please go on to the next page

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

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

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

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

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

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 31. Did you have a dry mouth? | 1 | 2 | 3 | 4 |
| 32. Did food and drink taste different than usual? | 1 | 2 | 3 | 4 |
| 33. Were your eyes painful, irritated or watery? | 1 | 2 | 3 | 4 |
| 34. Have you lost any hair? | 1 | 2 | 3 | 4 |
| 35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair? | 1 | 2 | 3 | 4 |
| 36. Did you feel ill or unwell? | 1 | 2 | 3 | 4 |
| 37. Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 38. Did you have headaches? | 1 | 2 | 3 | 4 |
| 39. Have you felt physically less attractive as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 40. Have you been feeling less feminine as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 41. Did you find it difficult to look at yourself naked? | 1 | 2 | 3 | 4 |
| 42. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 43. Were you worried about your health in the future? | 1 | 2 | 3 | 4 |
| 44. Have you had skin problems (e.g. itchy, dry)? | 1 | 2 | 3 | 4 |
| 45. Did itching of your skin bother you? | 1 | 2 | 3 | 4 |
| 46. Have you had a sore mouth or tongue? | 1 | 2 | 3 | 4 |
| 47. Have you had trouble swallowing? | 1 | 2 | 3 | 4 |

Please go on to the next page

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

| **During the past four weeks:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 48. To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 49. To what extent were you sexually active? (with or without intercourse) | 1 | 2 | 3 | 4 |
| 50. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |

# Appendix 5
# New York Heart Association Classifications

## Clinical Evaluation of Functional Capacity of Patients

| NYHA | Functional Class | Description | Objective Assessment |
|---|---|---|---|
| I | Mild | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea. | No objective evidence of cardiovascular disease. |
| II | Mild | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea | Objective evidence of minimal cardiovascular disease |
| III | Moderate | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea. | Objective evidence of moderately severe cardiovascular disease. |
| IV | Severe | Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. | Objective evidence of severe cardiovascular disease. |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors

## Tumor (T)

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ |
| Tis (DCIS) | DCIS |
| Tis (LCIS) | LCIS |
| Tis (Paget) | Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted. |
| T1 | Tumor ≤20 mm in greatest dimension |
| T1mi | Tumor ≤1 mm in greatest dimension |
| T1a | Tumor >1 mm but ≤5 mm in greatest dimension |
| T1b | Tumor >5 mm but ≤10 mm in greatest dimension |
| T1c | Tumor >10 mm but ≤20 mm in greatest dimension |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors (cont.)

## Tumor (T)

| | |
|---|---|
| T2 | Tumor >20 mm but ≤50 mm in greatest dimension |
| T3 | Tumor >50 mm in greatest dimension |
| T4 | Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)[a] |
| T4a | Extension to the chest wall, not including only pectoralis muscle adherence/invasion |
| T4b | Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma |
| T4c | Both T4a and T4b |
| T4d | Inflammatory carcinoma |

Reprinted with permission from AJCC: Breast. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 347–76.

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

Note: The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cut-off for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cut-off. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

[a] Invasion of the dermis alone does not qualify as T4.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors (cont.)

## Regional Lymph Nodes (N)

| Clinical | |
|---|---|
| NX | Regional lymph nodes cannot be assessed (e.g., previously removed) |
| N0 | No regional lymph node metastases |
| N1 | Metastases to movable ipsilateral level I, II axillary lymph node(s) |
| N2 | Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted |
| | OR |
| | Metastases in clinically detected [a] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases |
| N2a | Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures |
| N2b | Metastases only in clinically detected [a] ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases |
| N3 | Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement |
| | OR |
| | Metastases in clinically detected [a] ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases |
| | OR |
| | Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement |
| N3a | Metastases in ipsilateral infraclavicular lymph node(s) |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Regional Lymph Nodes (N)

| | Clinical |
|---|---|
| N3b | Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s) |
| N3c | Metastases in ipsilateral supraclavicular lymph node(s) |

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[a] Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pNX | Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study) |
| pN0 | No regional lymph node metastasis identified histologically |
| Note: ITCs are defined as small clusters of cells ≤0.2 mm, or single tumor cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by IHC methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated. | |
| pN0(i–) | No regional lymph node metastases histologically, negative IHC |
| pN0(i+) | Malignant cells in regional lymph node(s) ≤0.2 mm (detected by H&E or IHC including ITC) |
| pN0(mol–) | No regional lymph node metastases histologically, negative molecular findings (RT-PCR) |
| pN0(mol+) | Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC |
| pN1 | Micrometastases |
| | OR |
| | Metastases in 1–3 axillary lymph nodes |
| | AND/OR |
| | Metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| pN1mi | Micrometastases (>0.2 mm and/or >200 cells but none >2 mm) |
| pN1a | Metastases in 1–3 axillary lymph nodes, at least one metastasis >2 mm |
| pN1b | Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pN1c | Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected |
| pN2 | Metastases in 4–9 axillary lymph nodes |
| | OR |
| | Metastases in clinically detected [a] internal mammary lymph nodes in the absence of axillary lymph node metastases |
| pN2a | Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit $>2$ mm) |
| pN2b | Metastases in clinically detected[d] internal mammary lymph nodes in the absence of axillary lymph node metastases |
| pN3 | Metastases in $\geq 10$ axillary lymph nodes |
| | OR |
| | Metastases in infraclavicular (level III axillary) lymph nodes |
| | OR |
| | Metastases in clinically detected[c] ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes |
| | OR |
| | Metastases in $>3$ axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| | OR |
| | Metastases in ipsilateral supraclavicular lymph nodes |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pN3a | Metastases in ≥ 10 axillary lymph nodes (at least 1 tumor deposit >2 mm) |
| | OR |
| | Metastases to the infraclavicular (level III axillary lymph) nodes. |
| pN3b | Metastases in clinically detected [b] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; |
| | OR |
| | Metastases in > 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| pN3c | Metastases in ipsilateral supraclavicular lymph nodes |
| **Post-treatment ypN** | |
| Post-treatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "SN" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by AND. | |
| The X classification will be used (ypNX) if no yp post-treatment SN or AND was performed | |
| N categories are the same as those used for pN | |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

AND = axillary node dissection; H&E = hematoxylin and eosin stain; IHC = immunohistochemical; ITC = isolated tumor cells; RT-PCR = reverse transcriptase/polymerase chain reaction.

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[1] Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (SN) for "sentinel node," for example, pN0(SN).

[a] "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

[b] "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine-needle aspiration biopsy with cytologic examination.

## Distant Metastases (M)

| | |
|---|---|
| M0 | No clinical or radiographic evidence of distant metastases |
| cM0(i+) | No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other non-regional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases |
| M1 | Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm |

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**Post-treatment yp M classification.** The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pre-therapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Anatomic Stage/Prognostic Groups[a]

| Stage | T | N | M[c] |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| IA | T1[c] | N0 | M0 |
| IB | T0 | N1mi | M0 |
| | T1[c] | N1mi | M0 |
| IIA | T0 | N1[b] | M0 |
| | T1[c] | N1[b] | M0 |
| | T2 | N0 | M0 |
| IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| IIIA | T0 | N2 | M0 |
| | T1[c] | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| IIIB | T4 | N0 | M0 |
| | T4 | N1 | M0 |

## Appendix 6
## American Joint Committee on Cancer TNM Classification of Malignant (cont.)

| Stage | T | N | Mc |
|---|---|---|---|
| | T4 | N2 | M0 |
| IIIC | Any T | N3 | M0 |
| IV | Any T | Any N | M1 |

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Note: Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy. Post-neoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0cM0.

[a] T1 includes T1mi.

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

[c] M0 includes M0(i+); The designation pM0 is not valid; any M0 should be clinical. If a patient presents with M1 prior to NAST, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.

# *Appendix 7*
# *Correction of Predicted DLCO for Hemoglobin and Alveolar Volume*

*All DLCO measurements will be obtained as per the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines (MacIntyre et al. 2005). The predicted DLCO value should be corrected for both hemoglobin ($H_b$) and alveolar volume ($v_a$).*

*Pulmonary function test laboratories that follow the ATS/ERS guidelines should be able to provide the value for DLCO, corrected for $v_a$. A single breath $v_a$ may be used to obtain DLCO, corrected for va. Use the following equation to determine the predicted DLCO, corrected for $H_b$ and $v_a$:*

> *Predicted DLCO, corrected for $H_b$ and $v_a$ = [DLCO, corrected for $v_a$] × [1.7 × $H_b$ / (9.38 + $H_b$)]*

*Use the formula below to determine the percentage of predicted DLCO value (now corrected both for Hb and $v_a$):*

> ***% of predicted DLCO*** *(corrected for $H_b$ and $v_a$) =[actual DLCO / (predicted DLCO corrected for $H_b$ and $v_a$)] × 100*

**TITLE:** **PROTOCOL**

**A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2-NEGATIVE, EARLY STAGE BREAST CANCER**

| | |
|---|---|
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38/ NCT02273973 |
| **VERSION NUMBER:** | 1 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | 110184 |
| **TEST PRODUCT:** | GDC-0032 |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.D. |
| **SPONSOR:** | Genentech, Inc. |
| **DATE FINAL:** | See electronic date stamp below |

**FINAL PROTOCOL APPROVAL**

| **Approver's Name** | **Title** | **Date and Time (UTC)** |
|---|---|---|
| [redacted] | [redacted] | 23-Dec-2013 18:30:26 |

**Principal Investigators:**

[redacted]

| Author(s): | Affiliation |
|---|---|
| [redacted] | [redacted], Memorial Sloan Kettering Cancer Center, New York, NY, USA |
| | [redacted], Belgium |
| | [redacted], Diputació 256 4º1ª 08007 Barcelona, Spain |
| | [redacted], Genentech, South San Francisco, CA, USA |
| | [redacted], ABCSG, Nussdorfer Platz 8, 1190 Wien, Austria |
| | [redacted], ABCSG, Nussdorfer Platz 8, 1190 Wien, Austria |
| | [redacted], ABCSG, Austria |
| | [redacted], Genentech, South San Francisco, CA, USA |
| | [redacted], Genentech, South San Francisco, CA, USA |
| | [redacted] Spain |
| | [redacted] Spain |
| | [redacted], Genentech, South San Francisco, USA |
| | [redacted], Belgium |
| | [redacted] Belgium |
| | [redacted], Spain |
| | [redacted] Spain |
| | [redacted], Spain |

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| | |
|---|---|
| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2-NEGATIVE, EARLY STAGE BREAST CANCER** |
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38 |
| **VERSION NUMBER:** | 1 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | 110184 |
| **TEST PRODUCT:** | GDC-0032 |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.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 return the signed original of this form as instructed by your local study monitor. Please retain a copy for your study files.

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **A PHASE II RANDOMIZED, DOUBLE-BLIND STUDY OF NEOADJUVANT LETROZOLE PLUS GDC-0032 VERSUS LETROZOLE PLUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE/HER2- NEGATIVE, EARLY STAGE BREAST CANCER** |
| **PROTOCOL NUMBER:** | GO28888/BIG-3-13/SOLTI 1205/ABCSG 38 |
| **VERSION NUMBER:** | 1 |
| **EUDRACT NUMBER:** | 2013-000568-28 |
| **IND NUMBER:** | 110184 |
| **TEST PRODUCT:** | GDC-0032 |
| **PHASE:** | II |
| **INDICATION:** | Early stage breast cancer |
| **SPONSOR:** | Genentech, Inc. |

**Objectives**

**Efficacy Objectives**

The primary objective of this study is to evaluate the efficacy of letrozole plus GDC-0032 versus letrozole plus placebo in women with estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) early stage breast cancer, as measured by the following co-primary endpoints:

- Tumor overall objective response rate (ORR) by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in all enrolled patients and *PIK3CA* mutant (MT) patients
- Pathologic complete response (pCR) rate in breast and axilla (ypT0/Tis ypN0) by local evaluation in all enrolled patients and *PIK3CA* MT patients

The secondary efficacy objectives of this study are the following:

- Tumor objective response rate (ORR), assessed by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR ypT0/Tis ypN0) by local evaluation in *PIK3CA* wildtype (WT) patients

The following secondary objectives will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of locally assessed ORR using the following methods:
  - Breast ultrasound
  - Clinical breast exam (i.e., palpation)
  - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery.

- Compare the centrally assessed, preoperative endocrine prognostic index (PEPI) score upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo.
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment.
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

**Safety Objective**

The safety objective for this study is as follows:

- Evaluate the safety of letrozole plus GDC-0032 versus letrozole plus placebo

**Patient-Reported Outcome Objectives**

The patient-reported outcome (PRO) objectives for this study are as follows:

- Evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23)

**Exploratory Objectives**

The exploratory objectives for this study are as follows:

- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess whether biomarkers from tumor tissue or blood, including but not limited to somatic cancer associated mutations, PTEN expression, pro-survival pathways (such as PI3K/AKT, MAPK etc.), apoptotic markers, and levels of RNA and DNA expression are predictive of response
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to anti-tumor activity
- To assess concordance and percentage of *PIK3CA* mutation status from baseline biopsy and surgical specimen
- To assess emergence of resistance alleles from tumor tissue or blood
- To assess concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response
- To assess the pharmacokinetics and possible drug interaction between letrozole and GDC-0032 upon concomitant administration
- To assess the correlation of GDC-0032 drug levels and GDC-0032 related response (efficacy or adverse events [e.g., colitis, rash])
- To assess the influence of pharmacogenetic polymorphisms on GDC-0032 and/or letrozole on pharmacokinetics and response (either efficacy and/or adverse events)
- Compare the rates of breast-conserving surgery (BCS) and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo.

## Study Design

**Description of Study**

This is a two-arm, randomized, double-blind, multicenter, pre-operative study to evaluate the effect of combining letrozole and GDC-0032 versus letrozole and placebo in postmenopausal women with ER+/HER2- untreated, Stage I-III operable breast cancer whose primary tumors are $\geq$ 2 cm. Patients with cT4 or cN3 tumors are not eligible. Standard of care assessments/procedures (e.g., bilateral mammogram) performed within 28 days of Day 1 dosing do not need to be repeated for screening purposes.

All patients will undergo pretreatment tumor tissue acquisition (snap-frozen [optimal cutting temperature; OCT] and formalin-fixed paraffin-embedded cores [FFPE]). Two pretreatment FFPE core biopsies and one freshly frozen core biopsy must be obtained for all patients prior to beginning study drug treatment. Prior diagnostic FFPE core biopsies may be used for enrollment eligibility purposes. For the purpose of enrollment, ER, progesterone receptor (PR), and HER2 will be locally determined prior to beginning of study treatment. ER, PR, HER2, and

the percentage of Ki67-positive cells will also be centrally assessed, but the results do not have to be available prior to enrollment in the study. Remaining tissue will be retained for future translational studies. Pre-surgical sentinel lymph node biopsy (SLNB) is not allowed.

Patients will be randomized into one of the two treatment arms with a 1:1 randomization ratio. Letrozole at 2.5 mg will be dosed once daily plus either GDC-0032 at 6 mg or placebo on a 5 – days-on/ 2 – days-off schedule for a total of 16 weeks (see Figure 5). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

After confirmation of all the eligibility criteria, patients will be randomized to one of the treatment arms. A second biopsy will be performed on Day 15 (Week 3) for biomarker analyses. Biopsies should be performed at least 2 hours after GDC-0032 dose administration.

Randomization will be stratified according to 2 factors:

1. Tumor size (T1-T2 vs. T3)
2. Nodal status (cytologically positive vs. radiologically or cytologically negative)

The study will enroll approximately 330 patients at approximately 110 global sites.

At Weeks 1, 5, 9, 13, and 16 the primary breast tumor and axillary lymph nodes will be assessed by clinical breast examination (palpation and caliper measurement). Suspicion of progression based on clinical exam at any time should be further evaluated (Figure 6).

At Week 9, a breast ultrasound will be performed to ensure that there is no progressive disease and for the purpose of surgery planning. Suspicion of progressive disease on breast ultrasound should be confirmed by investigator-assessed breast MRI. Patients with primary disease not evaluable by ultrasound at baseline should be assessed by MRI at Week 9. Suspected progression in nodes should also be confirmed by fine needle aspiration (FNA) if these nodes had not been previously shown to be cytologically positive for cancer. Patients with progressive disease (as defined by modified RECIST, Appendix 3), can either proceed directly to surgery or be taken off of the study, according to the investigator's decision. If the patient goes off-study, every reasonable effort should be made to obtain a new biopsy prior to beginning another systemic treatment.

From Week 13, the patient will visit with the surgeon. The purpose of this visit is two-fold: tentative planning of the type of breast surgery to be performed (breast conservative vs. mastectomy) and scheduling the date for definitive surgery.

During Week 16, breast MRI will be done for the purpose of primary endpoint analysis. Clinical breast exam, breast ultrasound, and mammography will also be conducted prior to surgery for the purpose of the secondary endpoint analysis.

Blood sample for exploratory endpoint analysis will be collected at screening, at Week 3, and prior to surgery.

**Surgery**

Surgery will take place after at least 16 weeks of treatment, during Weeks 17 – 18. Surgery should be performed within 4 days after the last dose of GDC-0032, if possible, to best observe pharmacodynamic knockdown with GDC-0032 in the surgical specimen. Surgery may be delayed due to toxicity or other safety issues, upon discussion with the Medical Monitor (see Section 5.4.1) or recommendations from the Independent Data Monitoring Committee (IDMC; see below). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

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. Surgery specimens will be collected for histological examination to assess for pCR and for other endpoint analyses.

Following surgery, follow-up will proceed according to local standards of care. Adjuvant endocrine therapy and/or chemotherapy will be delivered as per the investigator's choice. Postoperative radiotherapy is required if BCS is performed. In the event of mastectomy, radiotherapy is to be administered according to local guidelines.

A postsurgery visit will be performed 4 weeks (+ 1 week) after surgery, and will mark the end of the study. Assessment of adverse events and general safety will be collected at this visit and the plan for future treatment will be recorded.

The patient should be evaluated at baseline and after Week 13 of treatment for planning of the surgical procedure (BCS or mastectomy), and both physician recommendation and final patient decision should be documented in the electronic Case Report Form (eCRF).

The co-primary efficacy endpoint, pathological complete response (pCR–ypT0/is, ypN0) will be established via a local review following completion of neoadjuvant therapy and surgery.

Please refer to the pathology manual for further guidance of evaluation for pCR and directions for sending a copy of the pathology report.

A schedule of assessments is provided in Appendix 1.

An Independent Review Facility (IRF) will be used to determine the tumor ORR via MRI. IRF procedures are detailed in the IRF charter.

**Number of Patients**

The study will enroll approximately 330 patients at approximately 110 global sites.

**Target Population**

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF) prior to any study-specific procedure
- Female patients
- Postmenopausal status and age ≥ 18 years. Postmenopausal status is defined as follows:
  - Age ≥ 60 years or
  - Age < 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment or
  - Prior bilateral oophorectomy (≥ 28 days prior to Day 1 of treatment)
- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor ≥ 2 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 ≥ 2 cm and designated as the "target" lesion for all subsequent tumor evaluations.
  - Stage I to operable Stage III breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms).
- ER-positive and HER2-negative breast cancer, as per local laboratory or regional definition
- Breast cancer eligible for primary surgery
- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for *PIK3CA* mutation status by central histopathology laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Fasting glucose ≤ 125 mg/dL
- Adequate hematological, renal, and hepatic function, as follows:
  - Absolute neutrophil count ≥ 1500/μL
  - Platelets count ≥100,000/μL
  - Hemoglobin ≥ 9 g/dL
  - Serum bilirubin ≤ 1.5 × the upper limit of normal (ULN)
  - Patients with known Gilbert's disease who have serum bilirubin ≤ 3 × ULN may be enrolled
- Aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase ≤ 1.5 × ULN

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation:

  $(140 - \text{age}) \times (\text{weight in kg}) \times (0.85)$
  $72 \times (\text{serum creatinine in mg/dL})$
- International normalized ratio (INR) $< 1.5 \times$ ULN and activated partial thromboplastin time (aPTT) $< 1.5 \times$ ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2–3 is required. If anticoagulation is required for a prosthetic heart valve, then INR should be between 2.5–3.5.
- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Ability and willingness to comply with study visits, treatment, testing, and to comply with the protocol, in the investigator's judgment

Exclusion Criteria

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

- Any prior treatment for primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer
- 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 sentinel lymph node biopsy prior to study treatment
- Type 1 or 2 diabetes requiring antihyperglycemic medication
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteric absorption
- History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis)
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF) $>$ 470 msec
- Clinically significant (i.e., active) cardiovascular disease, like uncontrolled hypertension, unstable angina, history of myocardial infarction, cardiac failure class II-IV (New York Heart Association, Appendix 5), or any other that in the judgment of the investigator could jeopardize patient safety or study outcomes
- 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
- Active infection requiring intravenous (IV) antibiotics
- Patients requiring any daily supplemental oxygen

- Clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis
- Known human immunodeficiency virus (HIV) infection
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications
- Significant traumatic injury within 3 weeks prior to initiation of study treatment
- Major surgical procedure within 4 weeks prior to initiation of study treatment
- Inability to comply with study and follow-up procedures
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

**Concomitant 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 7 days prior to screening to the study completion/discontinuation visit.

GDC-0032 was metabolized primarily by CYP3A4 in HLM and appeared to be a weak time dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low-to-moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC 0032 may be administered concomitantly with CYP3A4 substrates without the risk of a pharmacokinetic drug-drug interaction (DDI).

**Prohibited Therapy**

Prohibited therapy is as follows:

- **Anti-cancer therapy:** No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than letrozole permitted in this protocol) will be allowed.
- **Hormone replacement therapy**, **topical estrogens (including any intra-vaginal preparations), hormonal contraception, megestrol acetate, and selective estrogen-receptor modulators used with prophylactic intent**: If a patient is receiving these at the moment of registration, treatment should be discontinued prior to randomization.
- **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. Patients who develop osteopenia or osteoporosis in the follow-up period may receive bone-targeted therapy as per the clinician's discretion. Primary use of bisphosphonates as a prevention of bone metastasis or as a prevention of bone loss is prohibited.
- **Potent CYP3A4 inhibitors:** Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole and itraconazole) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If a strong CYP3A4 inhibitor is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.

**Length of Study**

The total duration of the study is expected to be approximately 24 months for enrollment, plus 5.5 months after last patient in.

**End of Study**

The end of the study is defined as the date when the last patient has her postsurgery visit.

## Outcome Measures

### Co-Primary Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

- Tumor ORR via centrally assessed breast MRI via modified RECIST (Appendix 3) in all enrolled patients and *PIK3CA* MT patients
- pCR rate in breast and axilla (total pCR) as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system (Appendix 6) by local evaluation in all enrolled patients and *PIK3CA* MT patients

### Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Tumor ORR, assessed by centrally assessed breast MRI via modified RECIST (Appendix 3) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR) by local evaluation in *PIK3CA* WT patients

The following secondary outcome measures will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of ORR, as measured by modified RECIST criteria (Appendix 3) using the following methods:
  - Breast ultrasound
  - Clinical breast exam (i.e., palpation)
  - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally assessed PEPI score upon treatment with letrozole plus GDC-0032 with letrozole plus placebo
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) yoT0/is, ypNX (breast pCR)

### Safety Outcome Measures

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0)
- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Serious adverse events
- Protocol-defined adverse events of special interest
- Clinically significant changes in vital signs and in clinical laboratory results during the adverse event reporting period (see Section 5.3.1)

### Patient-Reported Outcome Measures

The PRO outcome measures for this study are as follows:

- HRQoL, including side-effects of therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems), and patient functioning as measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ–C30) and the modified breast cancer module QLQ–BR23

### Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- ORR, pCR rate, and PEPI scores according to the decrease in Ki67 after 2 weeks of letrozole plus GDC-0032 and letrozole plus placebo.

- Expression of biomarkers before, during, and after therapy. These include, but are not limited to, the following:
  - PI3K pathway aberrations
  - Gene signatures, including intrinsic subtyping and PI3K pathway activity
  - Protein and phospho-protein markers and combinations
  - Mutations within cancer-associated genes
  - Copy number alterations in cancer-related genes
  - Plasma-based protein biomarkers
  - Circulating tumor DNA (ctDNA)
- Compare the rates of BCS and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo
- The relationship between GDC-0032 concentration and tumor response and/or drug safety response
- Letrozole concentrations with and without administration of GDC-0032
- The relationship between pharmacogenetic differences in drug metabolizing enzymes and transporters and other patient-specific covariates with PK of GDC-0032 or letrozole and/or drug response
- Changes from baseline to surgery in the apparent diffusion coefficient (ADC), a marker of tumor cellularity derived from diffusion-weighted MRI
- Concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response

**Investigational Medicinal Products**

Study treatment is neoadjuvant (pre-operative) therapy.

**Test Product**

The test product for this study is GDC-0032. Patients will receive an oral, daily dose of 6 mg GDC-0032 or placebo on a schedule of 5 days on/2 days off for a maximum of 16 weeks. Patients will take GDC-0032 at the same time of day ± 2 hours, unless otherwise instructed. Patients will be instructed as to the number of tablets to take.

Information on the formulation, packaging, handling, and administration of GDC-0032 are provided in the GDC-0032 Investigator's Brochure.

**Non-Investigational Medicinal Products**

**Letrozole**

Letrozole is a marketed product that is approved in the European Union and the United States for the treatment of hormone receptor-positive breast cancer. Based upon the different mechanisms of action of GDC-0032 and the well-established safety profile of letrozole, there are no expected overlapping, significant toxicities between letrozole and GDC-0032.

Patients will receive an oral, daily dose of 2.5 mg letrozole for 16 weeks (or until time of surgery at the investigator's discretion).

**Statistical Methods**

**Primary Analysis**

This study is designed for testing the effect of GDC-0032 on the two co-primary endpoints in all enrolled patients and in the *PIK3CA* MT patients and plans to enroll 330 patients in total. Assuming the *PIK3CA* mutation status will not be available (unknown) for approximately 10% of the patients and the prevalence of *PIK3CA* mutant is 40%, there will be approximately 120 patients in the *PIK3CA* MT cohort.

Given that the *PIK3CA* mutation status is not a stratification factor for randomization, there might be a possible imbalance between treatment arms within the *PIK3CA* MT cohort, which may reduce the statistical power in this cohort. To ensure the study provides sufficient statistical power even when the treatment assignment is imbalanced, the sample size was calculated based on a conservative scenario by assuming that the treatment assignment imbalance in

*PIK3CA* MT is 40% vs. 60%. The sample size was calculated based on a chi²-test using continuity correction (Ury and Fleiss 1980).

To control an overall two-sided, family-wise error rate under 20%, we use a two-sided significance level of 16% and 4% for the co-primary endpoints MRI ORR, and pCR, respectively.

Assuming 10% of the patients are unevaluable for the MRI ORR, approximately 300 enrolled patients and 108 patients in the *PIK3CA* MT cohort will be evaluable for analyses. This sample size allows us to detect an absolute percentage increase of 24% in MRI ORR rate in the GDC-0032 plus letrozole arm (64%) versus the letrozole-only arm (40%; Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at 80% power and 16% two-sided significance level. The minimal detectable difference for ORR is approximately 15%.

Assuming that all patients are evaluable for pCR (i.e., approximately 330 enrolled patients and 120 in the *PIK3CA* MT cohort), this sample size provides 80% power to detect an absolute percentage increase of 18% in pCR in the GDC-0032 plus letrozole arm (19%) versus the letrozole-only arm (1%, Smith et al. 2005; Ellis and Ma 2007) in the *PIK3CA* MT cohort at the 4% two-sided significance level. The minimal detectable difference for pCR rate is approximately 13%.

If the prevalence of the *PIK3CA* mutation is lower than assumed, if there is more substantial treatment assignment imbalance in the *PIK3CA* MT cohort than assumed, or there is an increased number of unevaluable patients for the MRI ORR, the sample size may be increased to obtain the level of power at 80%, and the enrollment may be limited to patients with *PIK3CA* MT.

**Secondary Analysis**

The secondary efficacy endpoints for this study are as follows:

- Tumor ORR after completion of study treatment, assessed by modified RECIST criteria by breast MRI in *PIK3CA* WT patients.
- Rate of pCR in breast and axilla (total pCR) after completion of study drug in *PIK3CA* WT patients.

These endpoint measures will be summarized by treatment arm and will be analyzed analogue to the primary efficacy endpoint.

The following secondary efficacy endpoints will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- ORR by clinical breast examination, mammography and breast ultrasound
- Ki67 values at baseline, Week 3, and surgery (centrally assessed)
- Change in Ki67 from baseline to Week 3; baseline to surgery, and Week 3 to surgery (centrally assessed)
- PEPI score (centrally assessed)
- Change in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluation of different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

These endpoint measures will be summarized by treatment arm and will be compared between the two treatment arms within each population based on appropriate statistical analyses: ORR will be compared using a Cochrane Mantel-Haenszel test, stratified by tumor size and nodal status; PEPI, Ki67, and tumor volume change will be compared by regression analyses, adjusted for tumor size and nodal status. All secondary endpoints will be tested at a two-sided type I error of 5%.

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

**Determination of Sample Size**

Please refer to the primary analysis in the Statistical Methods section.

**Interim Analyses**

An Independent Data Monitoring Committee (IDMC) will monitor accumulating patient safety data at a minimum of once every 6 months until the last patient has completed study treatment.

Additional details (e.g., IDMC members, communication, affiliations) will be provided in the IDMC charter.

The IDMC will conduct interim analyses to review the unblinded safety data after the first 20 patients have either 1) finished the 30-day follow-up visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery). The IDMC will create and review unblinded, pooled summaries of the safety and available PK summaries (all interim analyses). While this review is being conducted, patient accrual into the study will continue. The Medical Monitor may also request additional safety analysis and may call for additional meetings of the IDMC to review ongoing safety data.

The IDMC will share results from interim safety analyses with the study team. The study team will share interim safety results with study investigators as needed for the conduct of the study and the safety of the patients. Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections.

All available information of all enrolled patients with all available assessments at the respective timepoint will be included in the interim analyses.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ABCSG | Austrian Breast and Colorectal Cancer Study Group |
| ADC | apparent diffusion coefficient |
| AE | adverse events |
| AI | aromatase inhibitors |
| ALT | alanine transaminase |
| aPTT | activated partial thromboplastin time |
| ASCO-CAP | American Society of Clinical Oncology-College of American Pathologists |
| AST | aspartate aminotransferase |
| $AUC_{0-24}$ | area under the concentration–time curve from 0 to 24 hours |
| BCS | breast conserving surgery |
| BIG | Breast International Group |
| BUN | blood urea nitrogen |
| CD | compact disc |
| CI | confidence interval |
| $C_{max}$ | maximum plasma concentration observed |
| $C_{min}$ | minimum concentration under steady-state conditions within a dosing interval |
| cPR | confirmed partial responses |
| CRA | clinical research associate |
| CRO | contract research organization |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating tumor DNA |
| CTNeoBC | Collaborative Trials in Neoadjuvant Breast Cancer |
| DCR | data clarification request |
| DDI | drug-drug interaction |
| DLT | dose-limiting toxicity |
| DMP | data management plan |
| DVD | digital video disk |
| EC | Ethics Committee |
| $EC_{50}$ | 50% effective concentration |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |

| Abbreviation | Definition |
|---|---|
| EDC | electronic data capture |
| EGFR | epidermal growth factor receptor |
| ELISA | enzyme-linked immunosorbent assay |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ER+ | estrogen receptor-positive |
| E.U. | European Union |
| FFPE | formalin-fixed paraffin-embedded |
| FDA | Food and Drug Administration |
| FNA | fine needle aspiration |
| FSH | follicle stimulating hormone |
| GCP | good clinical practice |
| HbA1c | Glycosylated hemoglobin |
| HDL | high-density lipoprotein |
| HDPE | high-density polyethylene |
| HER2 | human epidermal growth factor receptor 2 |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HLA | human leukocyte antigen |
| HLM | human liver microsomes |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IHC | immunohistochemistry |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (application) |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IRF | Independent Review Facility |
| ISH | in situ hybridization |
| ITT | intent to treat |
| IV | intravenous |
| IxRS | interactive voice or web-based response system |
| LDL | low-density lipoprotein |
| LPLV | last patient, last visit |

| Abbreviation | Definition |
|---|---|
| MAPK | mitogen-activated protein kinase |
| MDD | minimum detected difference |
| MP | monitoring plan |
| MRI | magnetic resonance imaging |
| MT | mutant |
| MTD | maximum tolerated dose |
| mTOR | mammalian target of rapamycin |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NGS | next generation sequencing |
| NSCLC | non – small-cell lung cancer |
| nu/nu | immunocompromised nune (mice) |
| OCT | Optimal cutting temperature |
| ORR | objective response rate |
| pAKT | phosphorylated form of AKT |
| pCR | pathologic complete response |
| PD | progressive disease |
| PEPI | preoperative endocrine prognostic index |
| PFS | progression-free survival |
| PFT | pulmonary function test |
| PI3K | phosphatidylinositol-3-kinase |
| PIP2 | phosphatidylinositol-4,5-bisphosphate |
| PIP3 | phosphatidylinositol 3,4,5 trisphosphate |
| PK | pharmacokinetic |
| PO | oral |
| PR | progesterone receptor |
| PRO | patient-reported outcome |
| PTEN | phosphatase tensin homolog |
| QD | once daily |
| QLQ-BR23 | Quality of Life Questionnaire Breast Cancer Module |
| QLQ-C30 | Quality of Life Questionnaire Core 30 |
| QTcF | QT interval corrected using Fridericia's formula |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RT-PCR | real-time polymerase chain reaction |
| RFS | relapse-free survival |
| RPPA | reverse phase protein array |

| Abbreviation | Definition |
|---|---|
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SDV | source data verification |
| SLNB | sentinel lymph node biopsy |
| PFT | pulmonary function test |
| SOLTI | Spanish Breast Cancer Research Group |
| SOP | standard operating procedure |
| SmPC | summary of product characteristics |
| $t_{1/2}$ | terminal half-life |
| TGI | tumor growth inhibition |
| ULN | upper limit of normal |
| U.S. | United States |
| WBC | white blood cell |
| WT | wildtype |

# 1. BACKGROUND

## 1.1 BACKGROUND ON THE PHOSPHATIDYLINOSITOL-3-KINASE PATHWAY

Phosphatidylinositol-3-kinase (PI3K) is a lipid kinase involved in tumor cell proliferation, survival, and migration upon activation by growth factor receptors and integrins. PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3) (Cantley 2002), a second messenger involved in the phosphorylation of AKT and associated proteins in the AKT-mammalian target of rapamycin (mTOR) pathway (Guertin and Sabatini 2007 [29]). Activating and transforming mutations, as well as amplification, in the p110$\alpha$ subunit of PI3K are commonly found in solid and hematological tumors (Li et al. 1997 [38]). In addition, the PI3K-AKT pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling, the loss of the phosphatase tensin homolog (PTEN), or RAS mutations (Shayesteh et al. 1999 [58]; Cantley 2002 [11]; Massion et al. 2004 [42]; Wu et al. 2005 [68]).

## 1.2 BACKGROUND ON ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER

Breast cancer is the most frequently diagnosed cancer worldwide and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of total cancer deaths (Jemal et al. 2011 [34]). As a large proportion of breast cancer cases, especially in developed countries, are now diagnosed in early stages, they are amenable to cure with a stage-appropriate combination of surgery, systemic therapy (chemotherapy and/or hormonal therapy), and radiotherapy.

Estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer accounts for about 60%–70% of all breast cancers. However, not all ER+ breast cancers respond optimally to endocrine therapy (Davies et al. 2011 [15]). There are several mechanisms that can lead to primary and/or secondary hormonal resistance in ER+ breast cancer: decrease of ER expression, loss of ER expression, or upregulation of growth factor signaling pathways, like the epidermal growth factor receptor (EGFR)/HER2, the mitogen-activated protein kinase (MAPK), or the PI3K/AKT/mTOR pathways (Johnston 2009 [35]).

In the setting of ER+/HER2-negative breast cancer, the PI3K/AKT/mTOR pathway plays an important role in mediating hormonal resistance and is a viable therapeutic target to explore (Miller et al. 2010 [47]).

## 1.3 BACKGROUND ON THE PI3K/AKT/MTOR PATHWAY AND BREAST CANCER

Genes in the PI3K/AKT/mTOR signaling pathway are frequently mutated or amplified in breast cancer, especially in the ER+ subtype (Cancer Genome Atlas Network 2012 [10]). Molecular alterations of the PI3K/AKT/mTOR pathway include the following: (1) Mutations or amplifications in *PIK3CA*, the gene encoding the alpha catalytic subunit of PI3K (p110$\alpha$) (Saal et al. 2005 [52]; Wu et al. 2005 [68]); (2) Alterations in the tumor suppressor gene PTEN, either by loss of protein expression (PTEN null), inactivation mutations and/or epigenetic deregulation through promoter hypermethylation (García et al. 2004 [27]); (3) PDKP1 amplification and/or overexpression (Brugge et al. 2007 [9]); (4) AKT1 somatic gain of function mutations (Stemke-Hale et al. 2008 [61]) and AKT2 amplifications (Bellacosa et al. 1995 [7]). Overall, it is estimated that up to 70% of breast cancers can have some form of molecular aberration of the PI3K/AKT/mTOR pathway (CGAN 2012).

## 1.4 BACKGROUND ON REVERSING HORMONAL RESISTANCE BY INHIBITING THE PI3K/MTOR/AKT PATHWAY

In the setting of ER+ breast cancer, PI3K seems to play an important role in mediating hormonal resistance and may be a viable therapeutic target. Hyperactivation of this signaling pathway was proved to promote both *de novo* and acquired resistance to hormone therapy in ER+ breast cancer cell lines and xenograft models (Sabnis et al. 2007 [53]), and simultaneous blocking of the PI3K/AKT/mTOR pathway with everolimus and the ER pathway with letrozole enhances antitumor activity of either agent alone (Boulay et al. 2005 [8]). Importantly, a baseline protein signature of PI3K activation was found to be predictive of a poor prognosis after adjuvant endocrine therapy (Miller et al. 2010 [47]).

In the clinical setting, impressive results of the combination of exemestane and everolimus, an mTOR inhibitor, were reported in the BOLERO-2 trial (Baselga et al. 2009 [6]). This trial compared everolimus and exemestane with placebo and exemestane in 724 postmenopausal patients with ER+ advanced breast cancer who had experienced recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting and/or in advanced disease. Median progression-free survival (PFS) in the everolimus group was 6.9 months, as compared to 2.8 months in the placebo group. Hazard ratio (HR) for progression or death was 0.43, with a 95% confidence interval (CI) of $0.35-0.54$ ($p<0.001$), as per the investigator's assessment, and the magnitude of the effect was even greater as per central assessment (HR, 0.36, 95% CI, $0.27-0.47$; $p<0.001$). In the open-label Phase II TAMRAD trial, patients with aromatase inhibitors (AI) resistant metastatic breast cancer received tamoxifen plus everolimus or tamoxifen alone (Bachelot et al. 2012 [4]). The 6-month clinical benefit rate was 61% (95% CI, 47%–74%) with tamoxifen plus everolimus and 42% (95% CI, 29%–56%) with tamoxifen alone. Time to progression increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus

everolimus, corresponding to a 46% reduction in risk of progression with the combination (HR, 0.54; 95% CI, 0.36 – 0.81). Risk of death was reduced by 55% with tamoxifen plus everolimus versus tamoxifen alone (HR, 0.45; 95% CI, 0.24 – 0.81).

In the neoadjuvant setting, combination of letrozole and everolimus also resulted in improved responses over letrozole alone in patients with ER+ breast cancer (Baselga et al. 2009 [6]). In this study, 270 postmenopausal patients with operable ER+ breast cancer were randomly assigned to receive 4 months of neoadjuvant treatment with letrozole and either everolimus or placebo. The primary endpoint of the trial, clinical response by palpation, was higher in the everolimus arm than in the control arm (68.1% vs. 59.1%, $p = 0.062$), a statistically significant result (one-sided, $\alpha = 0.1$ level).

An important finding in trials with mTOR-targeting drugs like everolimus is that they produce a pharmacodynamic paradox: while inhibiting mTOR, they lead to an upregulation of the phosphorylated form of AKT (pAKT), resulting in feedback PI3K/AKT/mTOR pathway activation (Tabernero et al. 2009 [62]). This finding suggests that alternative pharmacologic strategies to effectively shut down the pathway upstream of AKT should be pursued. One of these strategies is inhibiting the PI3K/AKT/mTOR pathway at the level of PI3K.

## 1.5 BACKGROUND ON NEOADJUVANT THERAPY IN 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 and Smith 2003 [44]; Scholl et al. 1994 [56]; Semiglazov et al. 2004 [57]; Fisher et al. 2012 [26]; Wolff and Davidson 2000 [67]). The randomized studies evaluating neoadjuvant therapy as well as meta-analyses of these studies have shown that neoadjuvant therapy can improve breast conservation rates, decreasing the number of women obligated to undergo mastectomy (Mieog et al. 2007 [46]; Fisher et al. 2012). 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 [43]). The concept of neoadjuvant therapy is now well established and a standard treatment option for patients with early breast cancer. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis was recently conducted evaluating over 12,000 patients treated with neoadjuvant chemotherapy as part of clinical trials (Cortazar et al. 2012 [12]). The results of this meta-analysis confirmed an association of pathologic complete response [pCR] with favorable long-term outcomes in high-risk populations (i.e., HER2-positive, high-grade hormone receptor positive and triple negative subtypes), although the magnitude of pCR improvement predictive of the long-term survival benefits could not be determined. In September 2013, the Food and Drug Administration (FDA) granted accelerated approval

of Perjeta as part of a complete treatment regimen for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer in the neoadjuvant setting.

## 1.6 BACKGROUND ON GDC-0032

GDC-0032 is a potent selective inhibitor of Class I PI3K alpha, delta, and gamma isoforms, with 30-fold less potent inhibition of the beta isoform that is being developed as a therapy for human cancers. Nonclinical studies with GDC-0032 demonstrate that GDC-0032 inhibits proliferation of p110$\alpha$-mutant breast cell lines, inhibits tumor growth in human breast xenograft models harboring *PIK3CA* mutations, and results in a substantial reduction of PI3K pathway markers, including pAkt, pPRAS40, and pS6.

GDC-0032 has demonstrated activity in nonclinical models of *PIK3CA*-mutant breast tumors in vivo as a single agent and in combination with standard of care (e.g., paclitaxel or docetaxel) or endocrine therapies (e.g., letrozole or fulvestrant). GDC-0032 has a favorable in vitro and nonclinical in vivo absorption, distribution, metabolism, and elimination profile that has characteristics consistent with a compound that can be delivered orally to achieve clinical exposure similar to the nonclinical efficacy findings described herein. Additional studies, including 16-week toxicity studies in rats and dogs, phototoxicity studies, and an embryo-fetal development study, support the Phase II neoadjuvant trial with GDC-0032 in combination with endocrine therapy.

In vitro, single-agent GDC-0032 potency is also observed in cell lines that do not harbor *PIK3CA* mutations (Figure 1). In in vitro combination studies, the aromatase-expressing breast cancer cell line (MCF7X2.3.ARO) showed positive combination effects between GDC-0032 and endocrine therapies (see Figure 2). In this cell line, GDC-0032 alone caused growth inhibition (50% effective concentration [$EC_{50}$] = 95 nM). Effects on growth were also observed with letrozole and fulvestrant. Combined treatment of cells with GDC-0032 and letrozole caused dose-dependent inhibition of cell viability at lower concentrations of either GDC-0032 or letrozole resulting in enhanced activity for the combination. In addition, combination activity was demonstrated in the *PIK3CA* wild-type (WT) cell line ZR75-1 when GDC-0032 was added to either fulvestrant or tamoxifen endocrine therapies (combination with letrozole not available in this cell line). However, in vivo data in a *PIK3CA* WT model are not available, because these cell lines do not grow as xenografts.

**Figure 1 GDC-0032 Potency in Non-*PIK3CA* Mutant Breast Cancer Cell Lines**

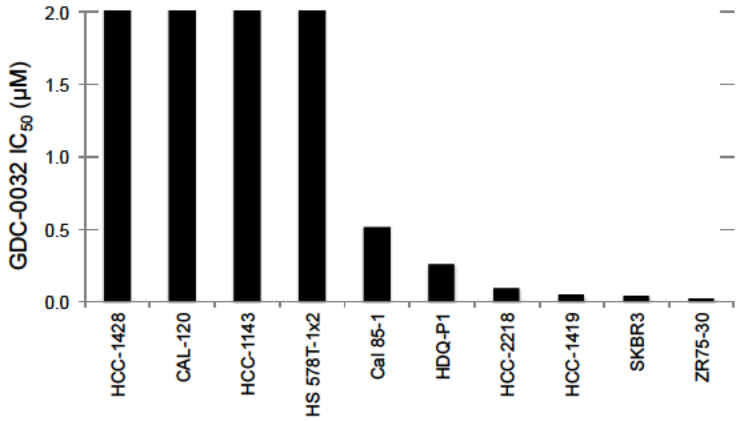
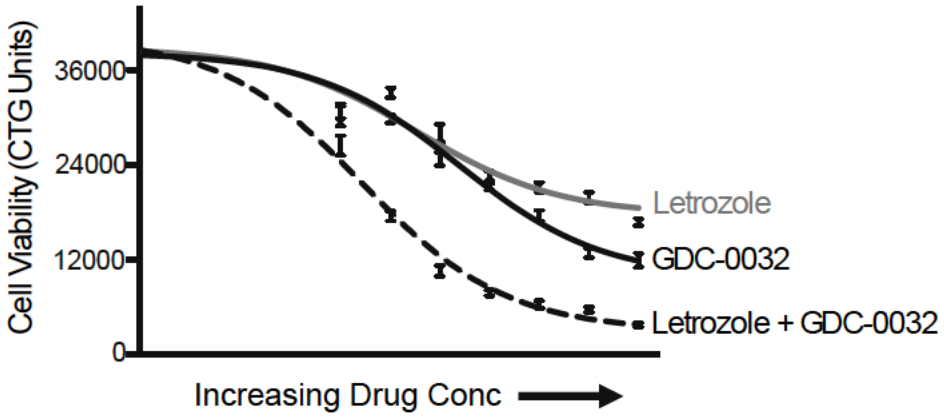


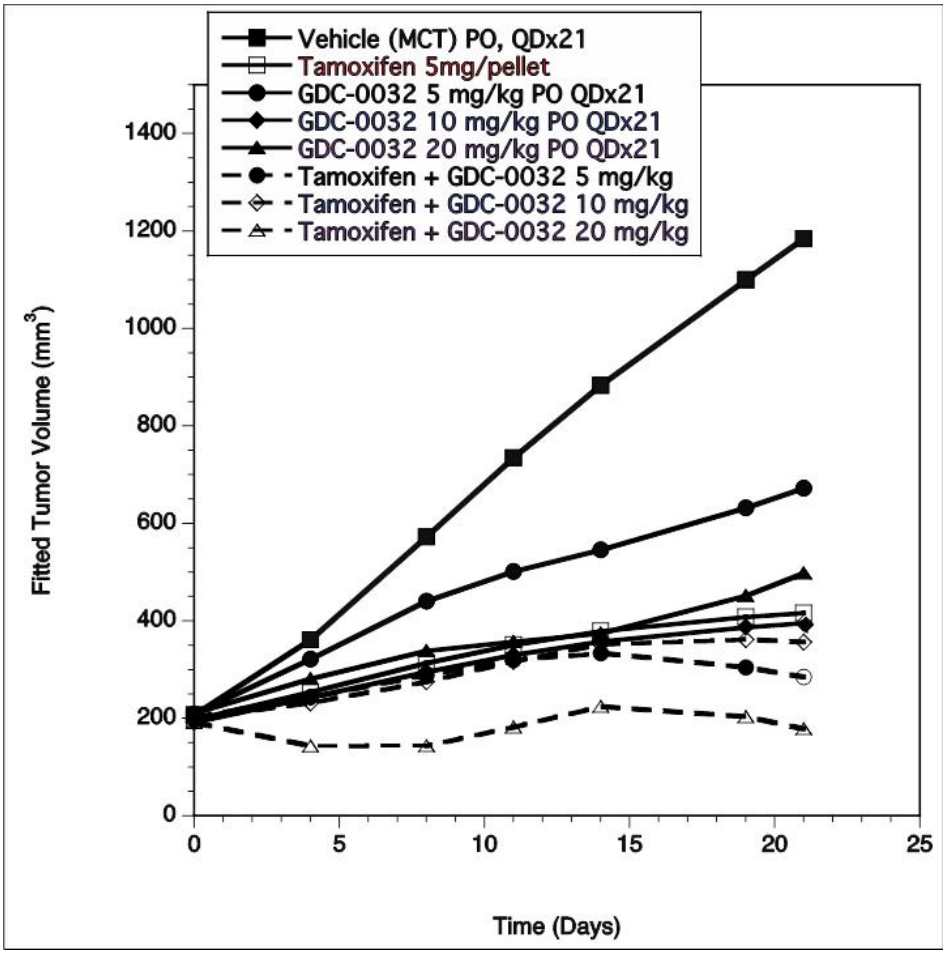

**Figure 2 Combination Effects between Letrozole and GDC-0032 in the Aromatase-Expressing MCF7.2x3 Breast Cancer Cell Line**




Conc = concentration.
MCF7X2.3.ARO (aromatase-expressing MCF7 cells) are sensitive to GDC-0032 in combination with endocrine therapies. Effects on viability are determined after 96 hours in culture.

Enhanced efficacy was demonstrated in combination with tamoxifen, another endocrine therapy used in the treatment of hormone receptor-positive advanced breast cancer. In this human MCF7-neo/HER2 (*PIK3CA* mutant [MT]) breast cancer xenograft model in immunocompromised nude (nu/nu) mice, administration of GDC-0032 at all doses tested (5, 10, or 20 mg/kg) in combination with tamoxifen (5-mg/pellet) resulted in greater efficacy (shown as a percentage of tumor growth inhibition [TGI]: 82% TGI, 80% TGI, and 102% TGI, respectively) compared to tamoxifen alone (73% TGI) or GDC-0032 as a single agent (71% TGI at 20 mg/kg) (see Figure 3). All combinations were well tolerated with no increase in mortality and no greater body weight loss than single agents alone.

**Figure 3 Efficacy of Tamoxifen in Combination with GDC-0032 in MCF7-Neo/Her2 Estrogen Receptor-Positive Mouse Xenografts**




QD = once daily; PO = oral gavage.

Vehicle was MCT (0.5% methycellulose/0.2% Tween-80).

Tamoxifen pellets (5 mg/pellet, 60-day release) were implanted on Day 0 of dosing (8 days post tumor implantation). Tumor volumes after QD oral administration of GDC-0032 for 21 days are depicted by dose group.

Please refer to the GDC-0032 Investigator's Brochure for additional nonclinical data for GDC-0032 supporting this clinical trial.

### 1.6.1 Toxicology

Please refer to the GDC-0032 Investigator's Brochure for details on the toxicology program to support this clinical trial.

## 1.7 SUMMARY OF CLINICAL DATA FOR GDC-0032

### 1.7.1 Clinical Safety Data with GDC-0032

As of 5 July 2013, a total of 144 patients have been treated with GDC-0032 either as single agent (90, 63%) or in combination with endocrine therapy (54, 37%).

GDC-0032 is currently in Phase I (Study PMT4979g). Study PMT4979g is an open-label, dose-escalation trial using a 3 + 3 design to assess the safety, tolerability, and pharmacokinetics of GDC-0032 administered orally daily for 28 days to patients with locally advanced or metastatic solid tumors and in combination with endocrine therapy in ER+ breast cancers. As of 5 July 2013, enrollment into the dose-escalation stage of Study PMT4979g had been completed with 34 patients enrolled at doses with a range of 3 to 16 mg daily. GDC-0032 was well tolerated in the first three cohorts (3, 5, and 8 mg), with no patients experiencing a dose-limiting toxicity (DLT). At the 16-mg dose level, 2 of the 11 safety-evaluable patients experienced a DLT (Grade 4 hyperglycemia and Grade 3 fatigue). At the 12-mg dose level, 1 of the 10 safety-evaluable patients experienced a DLT of Grade 3 acute renal failure. Although the single-agent GDC-0032 maximum tolerated dose (MTD) was not exceeded at the 16-mg dose level, the recommended GDC-0032 dose and schedule for the single-agent expansion cohorts is 9 mg daily on the basis of long-term safety data through multiple treatment cycles. As of the cutoff date, a total of 53 patients have been enrolled in the 9-mg daily dosing expansion cohorts.

As of 5 July 2013, adverse events that occurred in ≥ 10% of the 87 patients treated with daily single-agent GDC-0032 and were assessed as related to GDC-0032 were as follows: diarrhea (47%), hyperglycemia (38%), nausea (36%), fatigue (34.5%), decreased appetite (31%), rash (16%), stomatitis (13%), vomiting (13%), and mucosal inflammation (11.5%). Study–drug-related Grade 3 and 4 adverse events included hyperglycemia (9.4%), colitis (7.5%), pneumonitis (3.8%), rash (including maculopapular rash with or without itching, redness, and peeling) 5.7%, asymptomatic increased aminotransferase levels in the blood (1.9%), anemia (1.9%), increase in blood creatinine (1.9%), diarrhea (1.9%), fatigue (1.9%), hypokalemia (1.9%), hypophosphatemia (1.9%), pneumonia (1.9%) and stomatitis (1.9%).

As of 5 July 2013, a total of 27 patients have been enrolled in the expansion cohort of GDC-0032 at dose levels of 6 and 9 mg daily (19 patients at 6 mg, and 8 patients at 9 mg) daily in combination with letrozole (Cohort E). No DLTs were observed at either dose level. Adverse events that occurred in ≥ 10% of the 27 safety-evaluable patients assessed as related to GDC-0032 were diarrhea (67%), fatigue (30%), nausea (30%), decreased appetite (26%), hyperglycemia (26%), stomatitis (26%), dysgeusia (22%), mucosal inflammation (18.5%), rash (18.5%), asthenia (15%), pruritis (15%), vomiting (15%), dry mouth (11%), dry skin (11%) and muscle spasms (11%). Study – drug-related Grade 3 and 4 adverse events included diarrhea (11%), mucosal inflammation (7.4%), increased amylase in the blood (3.7%), increased aspartate aminotransferase (AST) in

the blood (3.7%), increased alkaline phosphate in the blood (3.7%), fatigue (3.7%), increased gamma-glutamyltransferase in the blood (3.7%), hyperglycemia (3.7%), hypokalemia (3.7%), increased lipase in the blood (3.7%), papilloedema (3.7%) and stomatitis (3.7%).

As of 5 July 2013, a total of 27 patients have been enrolled in the expansion cohort of GDC-0032 at dose levels of 6 and 9 mg daily (21 patients at 6 mg and 6 patients at 9 mg) in combination with fulvestrant (Cohort F). No DLTs were observed at either dose level. One patient has been enrolled in the Phase II part of the study with 6 mg GDC-0032 in combination with fulvestrant. Adverse events that occurred in $\geq$ 10% of the 27 patients and were assessed as related to GDC-0032 were diarrhea (46%), hyperglycemia (32%), nausea (32%), decreased appetite (25%), fatigue (25%), rash (21%), stomatitis (21%), asthenia (18%), muscle spasms (14%), vomiting (14%), dysgeusia (11%), gastroesophageal reflux disease (11%) and mucosal inflammation (11%). Study–drug-related Grade 3 and 4 adverse events included hyperglycemia (14%), diarrhea (7%), dyspnea (4%), flank pain (4%), hyponatremia (4%), neutropenia (4%), rash (4%) and vomiting (4%).

Please refer to the GDC-0032 Investigator's Brochure for additional information.

#### 1.7.1.1 Preliminary Pharmacokinetics

Pharmacokinetic (PK) data are available from 34 patients treated with GDC-0032 at 3, 5, 8, 12, and 16 mg in the ongoing Phase I/II clinical trial (Study PMT4979g). The cohort mean apparent clearance and the terminal half-life ($t_{1/2}$) following a single, oral dose of GDC-0032 had a range of 4.77–9.17 L/hour and 36.7–43.8 hours, respectively. Following daily oral dosing for 8 days, there was a 2- to 4-fold accumulation of GDC-0032. The pharmacokinetics of GDC-0032 appears to be dose linear and time-independent. Preliminary PK data from Cohort E suggest there is no drug-drug interaction (DDI) between letrozole plus GDC-0032. Mean plasma exposure of letrozole when given in combination with GDC-0032 (maximum concentration observed [$C_{max}$] = 0.407 μM and area under the concentration–time curve from 0 to 24 hours [$AUC_{0-24}$] = 8.01 μM*hr) was comparable with the historical single-agent exposure ($C_{max}$ = 0.495 μM and $AUC_{0-24}$ = 10.1 μM*hr) (Awada et al. 2008 [3]). Similarly, plasma concentrations of GDC-0032, when given in combination with letrozole, were within the range predicted by the population PK model. Therefore, letrozole plus GDC-0032 can be co-administered without the risk of a DDI.

GDC-0032 was metabolized primarily by CYP3A4 in human liver microsomes (HLMs) and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low to moderate potential to induce CYP3A4, preliminary data from the Phase I/II study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore,

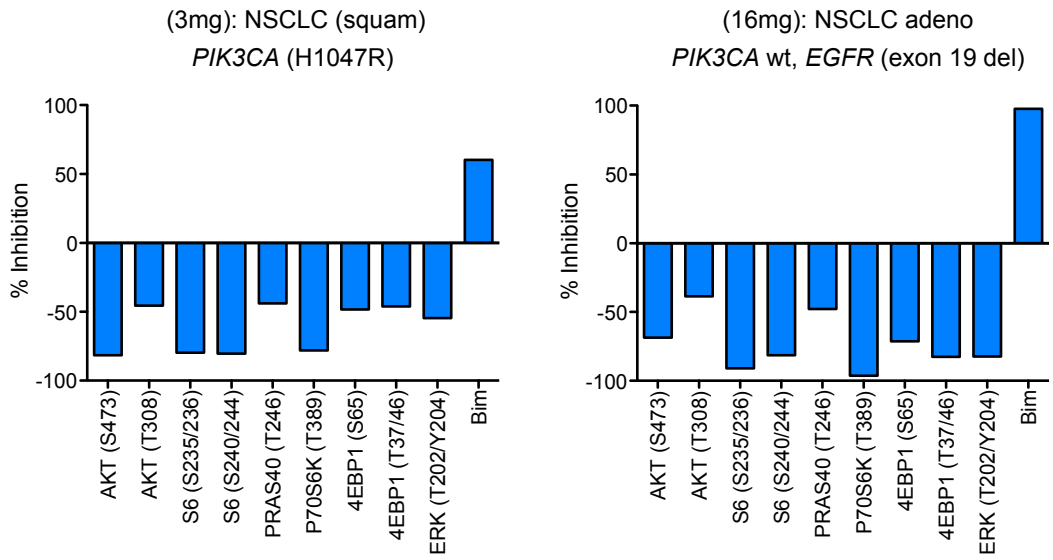
GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a PK DDI.

For additional details, refer to the GDC-0032 Investigator's Brochure.

### 1.7.1.2 Preliminary Pharmacodynamics

Paired tumor biopsies were obtained from both *PIK3CA* MT and *PIK3CA* WT non-small cell lung cancer (NSCLC) patients treated at either the 3-mg or 16-mg GDC-0032 dose level, respectively, at screening (pretreatment biopsy) and during Cycle 1 in Study PMT4979g (on-treatment biopsy). Inhibition of PI3K pathway markers, including decreases of >60% in pAKT and pS6 (compared with baseline), were demonstrated in these patients' paired tumor biopsies (see Figure 4).

**Figure 4 Decrease in PI3K Pathway Activation in Tumor Biopsies Observed upon GDC-0032 Treatment in Both *PIK3CA* MT and WT Tumors**




MT = mutant; NSCLC = non – small-cell lung cancer; WT = wild type.

As of 5 July 2013, metabolic partial responses via FDG-PET (≥20% decrease in maximum standardized uptake value) were observed in 23 out of 38 patients assessed (61%) and included patients from the lowest dose tested (3 mg). Thirteen of these 23 were breast cancer patients. Of the 13 response-evaluable patients treated with GDC-0032 plus letrozole, 10 patients (77%) had a partial metabolic response. Of the 15 response-evaluable patients treated with GDC-0032 plus fulvestrant, 11 (73%) had a partial metabolic response.

For additional details, refer to the GDC-0032 Investigator's Brochure.

## 1.8 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Cancer is one of the leading causes of death worldwide, with solid tumors accounting for the majority of these deaths. An estimated 1.38 million women across the world were diagnosed with breast cancer in 2008, accounting for 23% of all cancers diagnosed in women. Breast cancer is the most common cause of death from cancer in women worldwide, estimated to be responsible for almost 460,000 deaths in 2008 (Ferlay et al. 2010 [25]).

A neoadjuvant study in a similar patient population with the combination of letrozole and the mTOR inhibitor everolimus has already been completed (Baselga et al. 2009 [6]). Please refer to Sections 1.4, 1.5, and 3.3 for further rationale supporting the proposed trial design of combining GDC-0032 with letrozole in the neoadjuvant setting for this patient population. In postmenopausal women with hormone receptor-positive metastatic breast cancer, it is hypothesized that the combination of decreasing estrogen levels with letrozole and inhibition of the PI3K pathway with GDC-0032 may have improved anti-tumor activity as compared to endocrine therapy alone. This is supported by the nonclinical and clinical data outlined below.

GDC-0032 is a potent, selective small molecule inhibitor of Class 1 PI3K that is being developed by Roche/Genentech as an anti-cancer therapeutic agent. Activating and transforming mutations in the p110 alpha subunit of PI3K are commonly found in tumors. GDC-0032 has been shown to be a potent inhibitor of growth in various human cancer cell lines, and especially in nonclinical models of *PIK3CA* MT tumors. In addition, combination activity was demonstrated in the *PIK3CA* WT cell line ZR75-1 when GDC-0032 was added to either fulvestrant or tamoxifen endocrine therapies (combination with letrozole not available in this cell line).

GDC-0032 has also shown additive efficacy in combination with endocrine therapy in a hormone receptor-positive breast cancer xenograft model as outlined in Section 1.6. Nonclinical data support the investigation of GDC-0032 as a single-agent in solid tumors and in combination with endocrine therapy in patients with hormone receptor-positive, advanced breast cancer.

Available clinical data with single-agent GDC-0032 suggest that GDC-0032 has dose-linear pharmacokinetics with a half-life of approximately 37−44 hours. Pharmacodynamic markers of PI3K pathway inhibition upon treatment with GDC-0032 have been observed. These include decreases in phospho-S6 in platelet-rich plasma and decreases in F- flurodeoxyglucose-positron emission tomography uptake. Available clinical data also include multiple confirmed partial responses in patients treated with GDC-0032. These include a patient with *PIK3CA* MT lung adenocarcinoma treated at the 3 mg daily dose and another patient with *PIK3CA* MT, hormone receptor-positive, HER2-positive metastatic breast cancer treated at the 5 mg daily dose. In addition, a

patient with *PIK3CA* WT lung cancer treated at the 3 mg daily dose has had prolonged stable disease and remained on study for over 11 months. These data show that single-agent GDC-0032 doses below 6 mg have been shown to have anti-tumor activity. These aggregate data support the use of 6 mg in combination with letrozole.

Letrozole is a marketed product that is approved in the European Union (E.U.) and the United States (U.S.) for the treatment of hormone receptor-positive breast cancer. Based upon the different mechanisms of action of GDC-0032 and the well-established safety profile of letrozole, there are no expected overlapping, significant toxicities between letrozole and GDC-0032.

As of 5 July 2013, efficacy data are available for 24 patients treated with GDC-0032 in combination with letrozole; 3 patients (12.5%) had a partial response as best overall response, 2 of which were confirmed partial responses (cPRs) (1 cPR at 6 mg; 1 cPR at 9 mg). Of the 25 efficacy-evaluable patients treated with GDC-0032 in combination with fulvestrant, 7 patients (28%) had a partial response as best overall response, of which 3 were cPRs (1 cPR at 6 mg; 1 partial response at 9 mg). cPRs have been observed in both *PIK3CA* mutant and *PIK3CA* WT breast cancer patients. Maintenance of cPR has been observed in a patient who had a dose reduction from 6 mg to 3 mg for an adverse event. In addition, no additional safety concerns have been observed with GDC-0032 in combination with letrozole in the ongoing Phase I study compared to GDC-0032 given as single agent.

A number of clinically appropriate strategies to minimize risk to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, protocol design, and management guidelines. These will also be clearly highlighted and discussed in detail at investigator meetings and site visits. In addition, please refer to the GDC-0032 Investigator's Brochure for details regarding potential risks, associated precautions, and other relevant nonclinical and clinical safety information.

Due to the need to develop improved therapies to reverse or delay resistance to current endocrine therapy in HER2-negative, hormone receptor-positive breast cancer and on the basis of the clinical and nonclinical data available for GDC-0032, Genentech/Roche feels that the risk-benefit profile of GDC-0032 in combination with letrozole in postmenopausal patients with HER2-negative, hormone receptor-positive early stage breast cancer is favorable for proceeding with the proposed randomized Phase II clinical trial.

# 2. OBJECTIVES

## 2.1 EFFICACY OBJECTIVES

The primary objective of this study is to evaluate the efficacy of letrozole plus GDC-0032 versus letrozole plus placebo in women with ER+/HER2- early stage breast cancer, as measured by the following co-primary endpoints:

- Tumor overall objective response rate (ORR) by centrally assessed breast magnetic resonance imaging (MRI) via modified Response Evaluation Criteria in Solid Tumors (RECIST) in all enrolled patients and *PIK3CA* MT patients
- pCR rate in breast and axilla (ypT0/Tis ypN0) by local evaluation in all enrolled patients and *PIK3CA* MT patients

The secondary efficacy objectives of this study are the following:

- Tumor ORR, assessed by centrally assessed breast MRI via modified Response Evaluation Criteria in Solid Tumors (RECIST) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR ypT0/Tis ypN0) by local evaluation in *PIK3CA* WT patients

The following secondary objectives will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of locally assessed ORR using the following methods:
    - Breast ultrasound
    - Clinical breast exam (i.e., palpation)
    - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally assessed, preoperative endocrine prognostic index (PEPI) score upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo.
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment.
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR).

## 2.2 SAFETY OBJECTIVES

The safety objective for this study is as follows:

- Evaluate the safety of letrozole plus GDC-0032 versus letrozole plus placebo

## 2.3 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for this study are as follows:

- Evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23)

## 2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate changes in tumor cellular composition as assessed by diffusion-weighted MRI
- To assess whether biomarkers from tumor tissue or blood, including but not limited to somatic cancer associated mutations, PTEN expression, pro-survival pathways (such as PI3K/AKT, MAPK etc.), apoptotic markers, hormone receptor expression levels, and levels of RNA and DNA expression are predictive of response
- To determine whether inhibition of PI3K with GDC-0032 results in changes in downstream markers in tumor tissue and to examine the relationship to anti-tumor activity
- To assess concordance and percentage of *PIK3CA* mutation status from baseline biopsy and surgical specimen
- To assess emergence of resistance alleles from tumor tissue or blood
- To assess concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response
- To assess the pharmacokinetics and possible drug interaction between letrozole and GDC-0032 upon concomitant administration
- To assess the correlation of GDC-0032 drug levels and GDC-0032 related response (efficacy or adverse events [e.g., colitis, rash])
- To assess the influence of pharmacogenetic polymorphisms on GDC-0032 and/or letrozole on pharmacokinetics and response (either efficacy and/or adverse events)
- Compare the rates of breast-conserving surgery (BCS) and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo.

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF STUDY

This is a two-arm, randomized, double-blind, multicenter, pre-operative study to evaluate the effect of combining letrozole and GDC-0032 versus letrozole and placebo in postmenopausal women with ER+/HER2- untreated, Stage I-III operable breast cancer whose primary tumors are $\geq$ 2 cm. Patients with cT4 or cN3 tumors are not eligible.

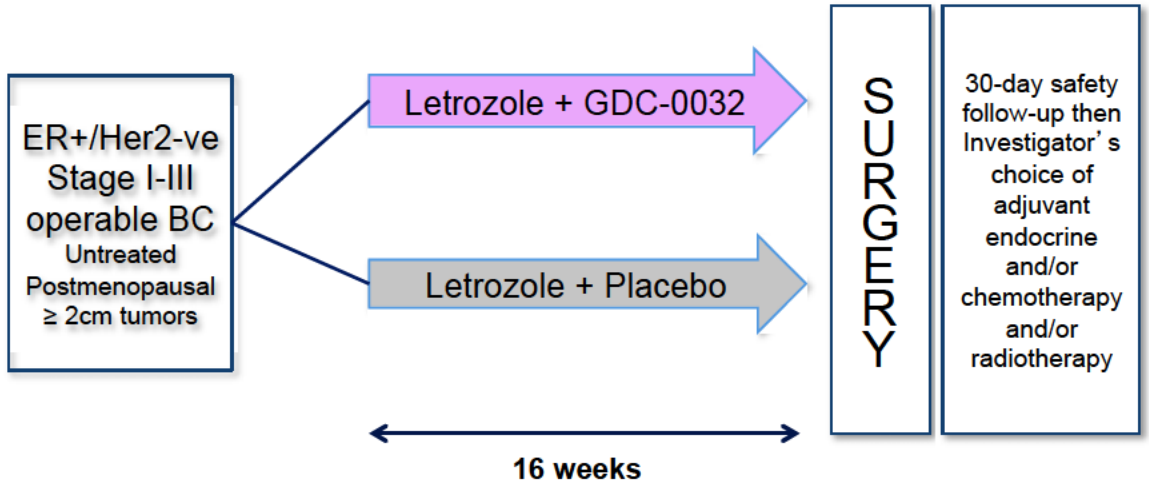
Standard of care assessments/procedures (e.g., bilateral mammogram) performed within 28 days of Day 1 dosing do not need to be repeated for screening purposes.

All patients will undergo pretreatment tumor tissue acquisition (snap-frozen [optimal cutting temperature; OCT] and formalin-fixed paraffin-embedded cores [FFPE]). Two pretreatment FFPE core biopsies and one freshly frozen core biopsy must be obtained for all patients prior to beginning study drug treatment. Tumor tissue from prior diagnostic FFPE core biopsies may be used for enrollment eligibility purposes. For the purpose of enrollment, ER, progesterone receptor (PR), and HER2 will be locally determined prior to beginning of study treatment. Remaining tissue will be retained for future translational studies. Pre-surgical sentinel lymph node biopsy (SLNB) is not allowed.

Patients will be randomized into one of the two treatment arms with a 1:1 randomization ratio. Letrozole at 2.5 mg will be dosed once daily plus either GDC-0032 at 6 mg or placebo on a 5 – days-on/ 2 – days-off schedule for a total of 16 weeks (see Figure 5). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

**Figure 5 Study Schema**

Letrozole 2.5 mg QD + GDC-0032 6 mg or placebo QD on a 5 – days-on/2 – days-off schedule




| | Pretreatment | Day 15 (Week 3) | Week 9 | Week 16 | Surgery (Week 17-18) |
|---|---|---|---|---|---|
| Tumor tissue | ● | ● | | | ● |
| MRI | ● | | ● | ● | |
| Breast U/S | ● | | ● | ● | |
| Mammogram | ● | | | ● | |

BC = breast cancer; ER + = estrogen receptor positive; MRI = magnetic resonance imaging; QD = once daily; U/S = ultrasound.

After confirmation of all the eligibility criteria, patients will be randomized to one of the treatment arms. A second biopsy will be performed on Day 15 (Week 3) for biomarker analyses. Biopsies should be performed at least 2 hours after GDC-0032 dose administration.

Randomization will be stratified according to 2 factors:

1. Tumor size (T1-T2 vs. T3)
2. Nodal status (cytologically positive vs. radiologically or cytologically negative)

The study will enroll approximately 330 patients at approximately 110 global sites.

At Weeks 1, 5, 9, 13, and 16 the primary breast tumor and axillary lymph nodes will be assessed by clinical breast examination (palpation and caliper measurement). Suspicion of progression based on clinical exam at any time should be further evaluated (Figure 6).

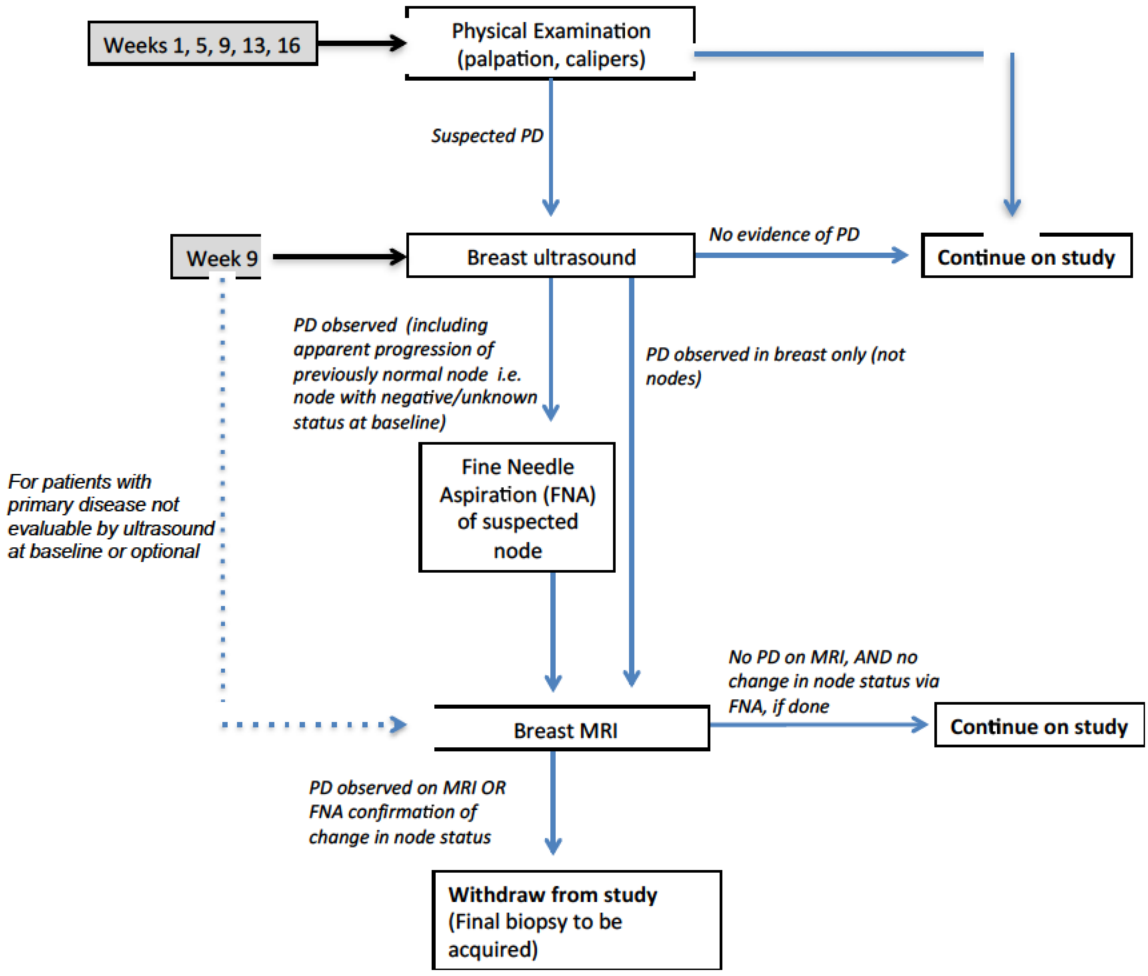
At Week 9, a breast ultrasound will be performed to ensure that there is no progressive disease and for the purpose of surgery planning. Suspicion of progressive disease on breast ultrasound should be confirmed by investigator-assessed breast MRI. Patients with primary disease not evaluable by ultrasound at baseline should be assessed by MRI at Week 9. Suspected progression in nodes should also be confirmed by fine needle aspiration (FNA) if these nodes had not been previously shown to be cytologically positive for cancer. Patients with progressive disease (as defined by modified RECIST, Appendix 3), can either proceed directly to surgery or be taken off of the study, according to the investigator's decision. If the patient goes off-study, every reasonable effort should be made to obtain a new biopsy prior to beginning another systemic treatment.

From Week 13, the patient will visit with the surgeon. The purpose of this visit is two-fold: tentative planning of the type of breast surgery to be performed (breast conservative vs. mastectomy) and scheduling the date for definitive surgery.

During Week 16, breast MRI will be done for the purpose of primary endpoint analysis. Clinical breast exam, breast ultrasound, and mammography will also be conducted prior to surgery for the purpose of the secondary endpoint analysis.

Blood sample for exploratory endpoint analysis will be collected at screening, at Week 3, and prior to surgery.

**Figure 6 Schematic Representing Confirmation of Progression**




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

### 3.1.1 Surgery

Surgery will take place after at least 16 weeks of treatment, during Weeks 17 – 18. Surgery should be performed within 4 days after the last dose of GDC-0032, if possible, to best observe pharmacodynamic knockdown with GDC-0032 in the surgical specimen. Surgery may be delayed due to toxicity or other safety issues, upon discussion with the Medical Monitor (see Section 5.4.1) or recommendations from the Independent Data Monitoring Committee (IDMC; see below). A maximum of 16 weeks of GDC-0032 can be administered. Letrozole can be continued up to surgery per the investigator's discretion.

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. Surgery specimens will be collected for histological examination to assess for pCR and for other endpoint analyses.

Following surgery, follow-up will proceed according to local standards of care. Adjuvant endocrine therapy and/or chemotherapy will be delivered as per the investigator's choice. Postoperative radiotherapy is required if BCS is performed. In the event of mastectomy, radiotherapy is to be administered according to local guidelines.

A postsurgery visit will be performed 4 weeks (+ 1 week) after surgery, and will mark the end of the study. Assessment of adverse events and general safety will be collected at this visit and the plan for future treatment will be recorded.

The patient should be evaluated at baseline and after Week 13 of treatment for planning of the surgical procedure (BCS or mastectomy), and both physician recommendation and final patient decision should be documented in the electronic Case Report Form (eCRF).

The co-primary efficacy endpoint, pCR (pCR–ypT0/is, ypN0) will be established via a local review following completion of neoadjuvant therapy and surgery.

Please refer to the pathology manual for further guidance of evaluation for pCR and directions for sending a copy of the pathology report.

A schedule of assessments is provided in Appendix 1.

An Independent Review Facility (IRF) will be used to determine the tumor ORR via MRI. IRF procedures are detailed in the IRF charter.

### 3.1.2 Independent Data Monitoring Committee

An IDMC will monitor accumulating patient safety data at a minimum of once every 6 months until the last patient has completed study treatment. Additional details (e.g., IDMC members, communication, affiliations) will be provided in the IDMC charter.

The IDMC will convene for an interim safety analysis to evaluate safety and pharmacokinetics after the first 20 patients have completed surgery and have had 30 days of follow-up. The IDMC will create and review unblinded, pooled summaries of the safety and available PK summaries (all interim analyses). While this review is being conducted, patient accrual into the study will continue. The Medical Monitor may also request additional safety analysis and may call for additional meetings of the IDMC to review ongoing safety data.

The IDMC will share results from interim safety analyses with the study team. The study team will share interim safety results with study investigators as needed for the conduct of the study and the safety of the patients. Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections.

## 3.2 END OF STUDY

The end of the study is defined as the date when the last patient has her postsurgery visit. The total duration of the study is expected to be approximately 24 months for enrollment, plus 5.5 months after last patient in.

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Conducting the Study in the Neoadjuvant Setting

Breast cancer is a heterogeneous disease, and not every breast tumor responds equally to a specific agent. Studies based on global gene expression analyses have provided additional insights into this complex scenario. Over the past 10 years, four major classes of breast cancer (Luminal A, Luminal B, HER2-enriched, and Basal-like) and a Normal Breast-like group have been identified and intensively studied (Perou et al. 2000 [49]; Sørlie et al. 2001 [60]). Known as the intrinsic subtypes of breast cancer, these groups of tumors have revealed critical differences in incidence, survival, and response to treatment. As genomic studies evolve, further sub-classifications of breast tumors are expected to emerge. Thus, a major challenge in breast cancer management is how to prospectively select patients who will derive the maximum benefit from a given drug regimen, minimizing unnecessary toxicities for patients with non-responsive disease.

Neoadjuvant therapy, a systemic therapy administered prior to breast cancer surgery, is now widely used in the 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 [43]), and the former offers clear advantages to patients, especially those with larger tumors. The tumor may shrink prior to surgery, thus increasing the rate of BCS (Coudert et al. 2006 [13]), and since the response to therapy can be monitored, the patient might be also spared further treatment with inactive medications.

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 treatment response at a biological level. Finally, the surgical specimen, if pCR is not reached, can be utilized as well. 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 (von Minckwitz and Fontanella 2013 [64]; Cortazar et al. 2012 [12]).

### 3.3.2 Rationale for Patient Population

Postmenopausal patients with HER2-negative, ER+, early stage breast cancer will be enrolled in this study. This patient population is usually treated with a combination of surgery, anti-hormonal therapy and/or chemotherapy, according to staging and biological features.

Recently, everolimus was approved by the FDA and European Medicines Agency in combination with exemestane for the treatment of advanced or metastatic breast cancer in patients after recurrence or progression following treatment with nonsteroidal AIs. In the neoadjuvant setting, a combination of letrozole and everolimus resulted in improved responses over letrozole alone in patients with ER+ breast cancer (Baselga et al. 2009 [6]).

Important findings in trials with drugs targeting mTOR, like everolimus, produce a pharmacodynamic paradox: while inhibiting mTOR, they lead to an upregulation of the pAKT, resulting in feedback PI3K/AKT/mTOR pathway activation (Tabernero et al. 2009 [62]). This finding suggests that alternative pharmacologic strategies to shut down the pathway upstream of AKT should be pursued. One of these strategies is to inhibit the PI3K/AKT/mTOR pathway at the PI3K level. PI3K-inhibitors are central regulators of the mTOR signaling pathway, and nonclinical findings show that PI3K-inhibitors and dual PI3K-mTOR inhibitors induce a greater amount of apoptosis than everolimus in estrogen-deprived in vitro models (Sanchez et al. 2011 [55]); therefore, it is hypothesized that PI3K-inhibitors may be active and demonstrate greater anti-tumor activity as compared to AIs alone in the neoadjuvant setting.

### 3.3.3 Rationale for Control Group

Aromatase inhibitors (AIs) have been found to be more effective than tamoxifen as a neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer.

Several trials have assessed the efficacy and safety of neoadjuvant endocrine therapy using AIs in patients with postmenopausal breast cancer (Eiermann et al. 2001 [18]; Smith et al. 2005 [59]; Ellis et al. 2011 [23]).

The P024 trial was a worldwide, prospective, randomized, multicenter trial that randomized 337 postmenopausal patients with ER+ breast cancer to receive either 4 months of neoadjuvant letrozole or tamoxifen (Eiermann et al. 2001 [18]). The primary endpoint of P024 was the percentage of patients in each treatment arm with objective response as determined by clinical palpation. Secondary endpoints included ORR determined by mammogram and ultrasound, and included the percentage of patients in each arm who had become eligible for BCS. The trial demonstrated a significantly higher clinical response rate for letrozole when compared to tamoxifen (55% vs. 36%; $p < 0.001$) in the intent-to-treat (ITT) population. An improved ORR for letrozole was also observed with ultrasound (35% vs. 25%; $p < 0.042$) and mammogram (34% vs. 16%; $p < 0.001$). The higher response rate assessed by clinical palpation translated into a significantly higher rate of women undergoing BCS in tumors that had initially been considered unsuitable for this procedure (45% vs. 35%; $p = 0.022$). Median time-to-response was 66 days in the letrozole group and 70 days in the tamoxifen group, and both treatments were well tolerated.

The IMPACT trial was a randomized, Phase II, double-blind, double-dummy, multicenter trial that randomly assigned 330 postmenopausal women with ER+ operable or locally advanced, potentially operable breast cancer in a 1:1:1 ratio to receive a daily dose of anastrozole 1 mg and tamoxifen placebo, tamoxifen 20 mg and anastrozole placebo, or a combination of tamoxifen 20 mg and anastrozole 1 mg for 12 weeks before surgery. The tumor ORR was assessed by both caliper and ultrasound. No significant differences in ORR in the ITT population between patients receiving tamoxifen, anastrozole, or the combination were seen. However, in a predefined analysis, there was a nonsignificant trend towards more patients requiring mastectomy at baseline actually receiving BCS with anastrozole than with tamoxifen (44% vs. 31%, respectively; $p = 0.23$); this difference became significant for patients deemed by their surgeon to be eligible for BCS after treatment (46% vs. 22%, respectively; $p = 0.03$). All treatments were well tolerated.

The ACOSOG Z1031 trial compared three AIs in a randomized, Phase II, neoadjuvant trial designed to select agents for Phase III investigations. Three hundred seventy-seven postmenopausal women with clinical Stage II to III ER+ breast cancer were randomly assigned to receive neoadjuvant exemestane, letrozole, or anastrozole. The primary endpoint was clinical response. No formal comparison between arms was pre-specified in the statistical plan. ORR was 62.9%, 74.8%, and 69.1% for the exemestane, letrozole and anastrozole arms, respectively. On the basis of clinical response rates, letrozole and anastrozole were selected for further investigation; however, no other differences in surgical outcome, PEPI score, or Ki67 suppression were detected. The BCS rate for mastectomy-only patients at presentation was 51%.

Results from these trials suggest that neoadjuvant endocrine therapy can be beneficial in postmenopausal patients with hormone-sensitive breast cancer, and that it offers an alternative to neoadjuvant chemotherapy.

### 3.3.4 Rationale for the Efficacy Outcome Measure of Response Rate Assessed by Magnetic Resonance Imaging

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, non-registrational, neoadjuvant trials in combination with endocrine therapy (Smith et al. 2005 [59]; Ellis and Ma 2007 [21]; Baselga et al. 2009 [6]).

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 computed tomography (CT) and mammography (Eisenhauer et al. 2009 [19]). 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 (Akazawa et al. 2006 [2]; Balu-Maestro et al. 2002 [5]; Yeh et al. 2005 [69]), including the I-SPY trial

(Hylton et al. 2012 [32]). For these reasons, ORR as assessed by breast MRI has been chosen as a co-primary endpoint for this trial.

#### 3.3.4.1 Rationale for Efficacy Outcome Measure of Pathologic Complete Response

pCR is a recognized efficacy endpoint of neoadjuvant trials, especially those with neoadjuvant chemotherapy, as it has been correlated with long-term outcomes, such as event-free survival (von Minckwitz and Fontanella 2013 [64]).

In trials of neoadjuvant hormonal therapy, pCR is an unlikely event. For instance, in the neoadjuvant trial comparing everolimus plus letrozole to letrozole, pCR rates were 1.4% and 0.8%, respectively (Baselga et al. 2009 [6]).

In the ongoing Phase I/II trial that combines letrozole with GDC-0032, tumor shrinkage has been observed, and some patients presented sustained partial responses. As pCR is a recognized indicator of activity to a given regimen, it would be useful to assess it as a co-primary efficacy endpoint of this trial. Furthermore, for the same trial size, this would represent a minimal increase in the minimum detected difference (MDD) of the co-primary endpoint for pCR ORR (from MDD of 12% to MDD of 13%).

In September of 2013, the FDA granted accelerated approval of Perjeta as part of a complete treatment regimen for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer in the neoadjuvant setting.

#### 3.3.4.2 Rationale for Ki67 Measurements

Ki67 is a well-established proliferation biomarker with prognostic value in ER+ breast cancer (Dowsett et al. 2011 [17]). Efficacy of endocrine therapy relies on induction of cell-cycle arrest, and during neoadjuvant treatment, Ki67 levels reflect the ability of endocrine agents to suppress proliferation (Smith et al. 2005 [59]; Ellis et al. 2011 [23]). In the neoadjuvant trial of letrozole with everolimus, by using the definition that patients with natural log (Ki67) $< 1$ at Day 15 have an antiproliferative response, 57% of everolimus-treated patients were responders vs. 30% in the placebo arm, with a significant p value of $< 0.01$ (Baselga et al. 2009 [6]). Furthermore, the mean reduction in the percentage of Ki67-positive tumor cells at Day 15 relative to baseline was greater in the everolimus-treated patients ($90.7\% \pm 3.2\%$) than in the placebo group ($74.8\% \pm 6.8\%$; $p = 0.0002$). In the IMPACT trial, Ki67 was assessed at baseline, on Day 15, and at surgery (Smith et al. 2005). For each treatment arm, the reduction in geometric mean Ki67 levels was significantly higher for anastrozole than for tamoxifen at both time points ($p = 0.004$, $p = 0.001$, respectively), but no differences were found between tamoxifen and the combination. In the ASCOSOG Z1031 trial (Ellis et al. 2011), although no data on Ki67 at Day 15 were available, no differences were found between treatments at baseline and at surgery (after $16 - 18$ weeks of therapy). The geometric mean percentage change in Ki67 for each treatment was similar between the arms (anastrozole 78%, exemestane 81.2%, and letrozole 87.1%).

The issue of whether Ki67 decrease at surgery or at any timepoint during treatment correlates with long-term efficacy outcomes has been addressed in the P024 trial (Eiermann et al. 2001 [18]). Treatment with letrozole led to higher, treatment-induced reduction of Ki67 levels in the tumor at surgery (87% reduction in the letrozole arm vs. 75% in the tamoxifen arm; analysis of covariance $p = 0.0009$) based on the 185 specimens with available data on Ki67 (Ellis et al. 2003 [20]). With a median follow-up of 61.2 months, low levels of Ki67 in the biopsy at the end of treatment were significantly associated with better relapse-free survival (RFS; HR 1.4 per natural log increase in the Ki67 value, 95% CI 1.2 – 1.6, $p < 0.001$), and breast cancer specific survival (HR 1.4, 95% CI 1.1 – 1.7, $p = 0.009$). Finally, in the IMPACT trial, higher Ki67 expression after 2 weeks of endocrine therapy was statistically significantly associated with lower RFS ($p = 0.004$), whereas higher Ki67 expression at baseline was not (Smith et al. 2005 [59]).

Importantly, the Ki67 suppression in these hormonal neoadjuvant trials mirrored efficacy outcomes in large adjuvant trials: adjuvant BIG1-98 trial ($n = 8,010$) showed the superior efficacy of letrozole over tamoxifen (Regan et al. 2011 [51]), similar to the neoadjuvant P024 trial ($n = 185$); the adjuvant ATAC trial ($n = 9,366$) showed that anastrozole was better than tamoxifen and the combination of anastrozole plus tamoxifen (Cuzick et al. 2010 [14]), similar to neoadjuvant IMPACT ($n = 259$); and the adjuvant MA27 trial ($n = 7,576$) showed similar efficacy of anastrozole and exemestane (Goss et al. 2013 [30]), mirroring neoadjuvant ACOSOG Z1031 ($n = 266$). These results suggest that a biological superiority hypothesis generated by a neoadjuvant study may help the design of future adjuvant hormonal therapy trials.

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

#### 3.3.4.3 Rationale for Using the Preoperative Endocrine Prognostic Index Score

In addition to Ki67, pathologic tumor size (T1 or T2 versus T3 or T4), node status (positive or negative), and the ER status (positive Allred score 3–8 versus negative Allred score 0–2) of the surgery specimen were also determined to have independent prognostic value for relapse and death after relapse in the P024 trial (Ellis et al. 2008 [22]). A PEPI score, prognostic for RFS, which weighs each of these factors according to their associated hazard ratios, was developed and subsequently validated in an independent data set from the IMPACT trial (Ellis et al. 2008). No relapses were recorded in either trial in patients with tumors classified as T1N0 and with a PEPI score of 0 (residual tumor with a Ki67 level $\leq 2.7\%$, and with maintained ER expression) or in the rare patient with a pCR.

In this trial, the PEPI score will be assessed centrally.

#### 3.3.4.4 Rationale for Assessing ORR by Clinical Breast Exam (Palpation), Mammography, and Breast Ultrasound

Objective overall response rate will also be assessed by clinical breast exam, mammography, and breast ultrasound during screening and prior to surgery. These data will allow for more direct comparison of results to other neoadjuvant trials with endocrine therapy as described in Section 3.3.3. The concurrent acquisition of ORR data with these techniques, in addition to MRI-based measures, will also provide valuable comparative information on these methods, which will be important for both future neoadjuvant studies and GDC-0032 clinical development.

#### 3.3.4.5 Rationale for Assessing Enhancing Tumor Volume by Breast Magnetic Resonance Imaging

As shown in the I-SPY trial, tumor volume measurements based on the percent of tumor with enhancing signal after contrast agent administration may be a more sensitive measure of response during neoadjuvant treatment than longest dimension measures (Hylton et al. 2012 [32]). However, there are no established response criteria for volumetric data, and the extrapolation of current one- and two-dimensional criteria to volumetric data based on a spherical model may not be appropriate given the range of tumor morphologies expected in this population of patients (Loo et al. 2011 [40]). Additionally, there are only very limited data on the clinical relevance of any particular range in change in tumor volume during the course of neoadjuvant treatment. For these reasons, changes in enhancing tumor volume as measured by breast MRI will be a secondary endpoint in the trial.

### 3.3.5 Rationale for Independent Review Facility

Due to the relatively novel nature of using MRI as an imaging endpoint, a central assessment by an IRF for the co-primary endpoint of response rate via MRI will be performed to ensure consistency across all sites participating in the study.

### 3.3.6 Rationale for Interim Safety Review

The first 20 patients will be assessed for safety following surgery and 30 days beyond. This will allow the IDMC to review all safety data during the treatment period and to evaluate any surgery complications that may be attributed to GDC-0032.

### 3.3.7 Rationale for GDC-0032 Dosage

As of 5 July 2013, 34 patients have been enrolled into the dose-escalation stage of Study PMT4979g, and 56 patients have been enrolled into the single-agent expansion cohorts at 9 mg in Stage 2 (Cohorts A-D and G). Five dose-escalation cohorts (i.e., 3, 5, 8, 12, and 16 mg daily) were tested. The maximal administered dose was 16 mg. To obtain more safety data on long-term tolerability, the recommended single-agent dose and schedule for the single-agent GDC-0032 expansion stage is 9 mg daily.

In Study PMT4979g, as of the 5 July 2013 data cutoff date, there were 87 safety evaluable patients treated with single-agent GDC-0032 (3 – 16 mg daily). A total of 97%

of patients experienced at least one adverse event per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 (NCI CTCAE v4.0). The most frequently reported adverse events, occurring in ≥10% safety-evaluable patients regardless of causality, were diarrhea (55%), fatigue (49%), nausea (47%), decreased appetite (39%), hyperglycemia (38%), vomiting (28%), dizziness (22%), rash (22%), dyspnea (18%), hypokalemia (18%), pyrexia (17%), cough (16%), anemia (13%), dehydration (13%), headache (13%), stomatitis (13%), AST increased (12%), mucosal inflammation (12%) and pruritis (10%).

As of 5 July 2013, 54 patients have been treated with GDC-0032 in combination with endocrine therapy with either letrozole (Cohort E) or fulvestrant (Cohort F) at either 6 mg or 9 mg dose levels. No DLTs were observed during dose escalation in either Cohorts E or F. Expansion cohorts at the 6-mg dose level were enrolled to obtain more safety data on long-term tolerability. Fifty (93%) of the 54 safety-evaluable patients experienced at least one adverse event that was assessed as related to GDC-0032.

Of the 54 patients, 17 patients were treated with GDC-0032 plus letrozole. Adverse events that occurred in ≥10% of patients that were assessed as related to GDC-0032 (6mg and 9mg) were diarrhea (67%), nausea (33%), fatigue (30%), rash (30%), hyperglycemia (26%), decreased appetite (26%), stomatitis (26%), dysgeusia (22%), mucosal inflammation (19%), asthenia (15%), vomiting (15%), pruritis (15%), muscle spasms (11%), dry skin (11%), and dry mouth (11%).

Of the 19 efficacy-evaluable patients treated with GDC-0032 in combination with letrozole, one patient at 6 mg had a cPR. The *PIK3CA* mutation status of this patient is unknown. Since efficacy has been observed at 6 mg, and the long-term safety suggests that 6 mg is better tolerated, the neoadjuvant study will utilize 6 mg GDC-0032 in combination with letrozole.

Of the 27 efficacy-evaluable patients treated with GDC-0032 in combination with fulvestrant, 2 confirmed partial responses were observed at 6 mg and 1 confirmed partial response at 9 mg.

Colitis has been observed with an incidence rate of 6.2% (10/160 patients). The time (from the first dose of study treatment) to onset of colitis ranged from approximately 82 – 248 days as either a single agent or in combination with letrozole or fulvestrant. Most of the colitis cases have been observed at the 9-mg dose level or higher. Most of the colitis cases have been observed at the 9-mg dose level or higher. To mitigate the late-onset adverse events, such as colitis, an intermittent dosing schedule will be applied. With the 40-hour half-life, a limited impact on efficacy is anticipated. PK modeling has shown that a schedule of 5 days on/2 days off will maintain GDC-0032 drug exposure levels within an efficacious range as assessed by various breast cancer cell lines. There has also been data presented for another PI3K inhibitor BKM120 with a similar half-life in combination with letrozole in a Phase Ib study that demonstrated improved tolerability

with similar efficacy for a schedule of 5 days on/2 days off as compared to daily continuous dosing of the PI3K inhibitor (Mayer et al. 2012 [45]).

### 3.3.8 Rationale for Biomarker Assessments

Breast cancer is a heterogeneous disease, and *PIK3CA* mutations have been shown to vary among patients (CGAN 2012). Therefore, all patients may not equally likely benefit from treatment with GDC-0032. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with *PIK3CA*-driven pathogenesis who are most likely to respond to GDC-0032. Pharmacodynamic biomarkers will be assessed to assess the biologic activity of the addition of GDC-0032 to letrozole.

It has been suggested that not all molecular alterations in the PI3K/AKT/mTOR pathway result in pathway activation. In a comprehensive analysis of tumors from 850 breast cancer patients, protein markers of PI3K/AKT/mTOR pathway activation (pAKT, pS6, and p4EBP1) correlated strongly with *INPP4B* and PTEN loss, to a degree with *PIK3CA* amplification, but were not elevated in *PIK3CA*- MT luminal A cancers (CGAN 2012). This apparent disconnect between the presence of *PIK3CA* mutations and biomarkers of pathway activation had been previously noted (Loi et al. 2010 [39]), and stress the need to find innovative and robust predictive biomarkers to PI3K/AKT/mTOR pathway inhibiting agents (Saini et al. 2013 [54]).

Next generation sequencing (NGS) techniques, like deep genome sequencing, may offer a unique opportunity to identify such biomarkers of response. For example, using whole genome sequencing, a two base-pair deletion in the *TSC1* gene was found in a metastatic bladder cancer patient with a prolonged response ($>2$ years) to everolimus as single agent (Iyer et al. 2012 [33]). Among 13 additional bladder cancer patients treated with everolimus in the same trial, those with *TSC1* mutant tumors remained on therapy longer than those with WT tumors (7.7 vs. 2.0 months, $p=0.004$), suggesting that mTORC-1 directed therapies may be most effective in cancer patients whose tumors harbor *TSC1* somatic mutations. Similar approaches could be of great value when analyzing responses to agents targeting the PI3K/AKT/mTOR pathway, especially in the neoadjuvant setting.

In addition to mutational activation of proteins, levels of RNA and DNA can also activate the PI3K pathway. For example, increases in DNA copy number in receptor tyrosine kinases such as FGFR1/2 and IGF-1R, which occur at some frequency in breast cancer, can activate downstream PI3K pathway. Hormone receptor positive breast cancer can be divided into luminal A and luminal B subtype, with the luminal B subtype displaying a higher proliferative index. Therefore, profiling the RNA and DNA expression of tumors will allow intrinsic subtyping of patients enrolled onto study. In addition, PI3K transcription activation signatures may identify additional patients who could respond to PI3K inhibitors outside of *PIK3CA* mutations.

The use of circulating tumor DNA (ctDNA) to monitor response to treatment is an area of great interest. It could allow for an early, non-invasive, and quantifiable method for use in the clinical setting to identify candidates for specific therapies and monitoring of disease mutation status over time (Higgins et al. 2012 [31]). The neoadjuvant setting is ideal to prospectively test these approaches.

### 3.3.9 Rationale for Day 15 Biopsy

On-study biopsies can provide valuable information regarding target engagement and downstream pathway suppression. Assessing how GDC-0032 interacts with letrozole in this previously untreated patient population provides a unique opportunity to understand the interaction between two anti-cancer molecules. When available, FFPE tumor samples will be assessed for pathway modulation using immunohistochemistry (IHC) methodologies, and fresh frozen OCT samples will be assessed using reverse phase protein array (RPPA) technologies, or equivalent. Measurement of Ki67 after 2 weeks of continuous letrozole and GDC-0032 combination treatment versus letrozole and placebo will give a good benchmark to prior neoadjuvant studies that demonstrated a larger decrease in Ki67 at this 2-week timepoint for a combination of letrozole and everolimus as compared to letrozole and placebo (Baselga et al. 2009 [6]). This Day 15 biopsy will also be useful in identifying potential biomarkers that may help predict a tumor response for patients treated with GDC-0032.

### 3.3.10 Rationale for Collection of Blood Sample for the Detection of Plasma Protein Biomarkers

Emerging evidence indicates that increases in levels of systemic cytokines and chemokines, such as receptor tyrosine kinase growth factors, can attenuate response to drugs, particularly targeted agents such as GDC-0032 (Wilson et al. 2012 [66]). Assays to assess the expression of soluble, systemic cytokines and chemokines from the plasma of patients will be carried out using ELISA-based mass spectrometry or equivalent methodologies.

### 3.3.11 Rationale for Collection of Blood Sample for DNA Sequencing to Identify Mutations in Plasma

There is increasing evidence that circulating DNA obtained from blood specimens of cancer patients is representative of the DNA and mutational status of tumor cells (Diehl et al. 2008 [16]; Maheswaran et al. 2008 [41]). Assays are available that can detect the major PI3K mutations (and other cancer-related genes) in plasma, and results from this analysis will be correlated with tumor specimens.

### 3.3.12 Rationale for Collection of Blood Sample for Next Generation Sequencing

Next generation sequencing (NGS) technologies generate a large quantity of sequencing data. Tumor DNA can contain both reported and unreported chromosomal alterations due to tumorigenesis process. To help control for sequencing calls in

previously unreported genomic alterations, a normal blood sample will be taken during pre-screening to determine whether the alteration is somatic or germline.

### 3.3.13 Rationale for Pharmacokinetic Sample Collection Schedule

PK samples will be collected from early breast cancer patients in this study to assess the pharmacokinetics of GDC-0032 and possible DDI between letrozole and GDC-0032 in this population. Considering the lack of DDI between GDC-0032 and letrozole upon concomitant administration in the 24 metastatic breast cancer patients in the Phase I study (preliminary data), this drug interaction in early breast cancer patients is unlikely. Hence, extensive PK sample collection is not needed; sparse PK sampling from patients enrolled in this study is adequate. The proposed PK sample collection schedule will also enable assessment of a concentration and response relationship to better understand the following: pharmacokinetics/pharmacodynamics (efficacy), PK/safety correlation, and population pharmacokinetics. Additional PK samples may be collected for safety concerns (e.g., severe adverse event) in order to better characterize drug levels in these patients at the time of the adverse event.

### 3.3.14 Rationale for the Collection of DNA for Exploratory Pharmacogenetic Polymorphisms

One sample (approximately 3 mL of whole blood) will be collected from all patients using K3-EDTA collection tubes. Samples will be used for the evaluation of genetic polymorphisms of drug metabolic enzymes including, but not limited to, CYP2C9, CYP3A4/5, and UGT1A1, and transporters (e.g., OATP1B1) and for genetic variants which could contribute to potentially drug-related rash and/or colitis safety assessments (including but not limited to human leukocyte antigen [HLA]). For sample handling procedures, storage conditions, and shipment instructions, see the laboratory manual. Only in circumstances where there is concern for collection of this genetic material for above evaluations, can this assessment be considered not mandatory as part of study assessments in this study. Results of any analyses from these samples will be reported outside the clinical study report.

It is established that genetic variants of drug-metabolizing enzymes and transporters can affect the pharmacokinetics of drugs, which affects their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1, which facilitates the metabolism and excretion of SN 38 (the active metabolite of irinotecan), are at higher risk for adverse effects associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006 [48]). Preliminary results from in vitro metabolism studies with GDC-0032 suggest that they are partially metabolized by multiple Phase I cytochrome P450 enzymes, including CYP3A4. Although in vitro studies can help elucidate the roles of enzymes in the metabolism of the drug, these results are not always predictive of in vivo metabolism for a number of reasons, such as differences in drug concentrations that the enzymes encounter in vitro and in vivo. For this reason, a blood sample for DNA isolation is proposed to be

collected from all patients in this study for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics or response to GDC-0032. The decision to analyze the samples will be based on a review of the pharmacokinetics and response data. Most recently, the role of HLA has been demonstrated to play an important role in the development of drug-induced rash for some drugs (carbamazepine, abacavir, and allopurinol). Therefore, evaluation of genetic variants of genes that may regulate the immune response (including but not limited to HLA) may also be investigated to characterize unusual safety responses that are not predicted by GDC-0032 pharmacokinetics.

The analysis will be performed on identifiable DNA samples, because it is necessary to link a patient's PK data with genotype. This analysis would be restricted to the evaluation of genes that may be involved in the pharmacokinetics of GDC-0032, drug metabolism, disposition, or elimination and/or response of patients who develop severe adverse reactions such as colitis or rash. Samples may be stored and analyzed up to 15 years after the completion of the study, at which time all DNA samples collected for this analysis will be destroyed.

### 3.3.15 Rationale for Patient-Reported Outcome Assessments

A PRO is "any report on the status of a patient's health condition that comes directly from the patient, without any interpretation of the patient's response by a clinician or anyone else" (FDA Guidance for Industry 2007 [24]). PRO measures are able to contextualize a patient's experience on trial, elucidating symptom and treatment burden. Since early breast cancer is often asymptomatic, the PRO objective is to evaluate and compare PROs of treatment-related symptoms, patient functioning, and the health-related quality of life between treatment arms (Lemieux et al. 2011 [37]).

The EORTC QLQ-C30 and associated breast cancer module, QLQ-BR23, were selected because they were specifically developed to assess the most salient constructs and experiences with breast cancer and its treatment. The EORTC QLQ-C30 is a widely and frequently used PRO measure in oncology trials that contains a global health status scale, functional scales (physical, role, emotional, cognitive, and social), and general cancer symptom scales/items with a recall period of 'the past week.'

The second measure, the QLQ-BR23, is a breast cancer specific modular supplement to the EORTC QLQ-C30, and includes additional functioning scales and symptom scales/items relating to breast cancer.

These instruments demonstrate strong psychometric properties, of both reliability and validity, and meet the requirements for this study (EORTC QLQ-C30 Scoring Manual, 1999). Therefore, PRO data will be collected from patients using the EORTC QLQ-C30 and modified QLQ-BR23 (Quinten et al. 2009 [50]).

## 3.4 OUTCOME MEASURES

### 3.4.1 Efficacy Outcome Measures

#### 3.4.1.1 Co-Primary Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

- Tumor ORR, via centrally assessed breast MRI via modified RECIST (Appendix 3) in all enrolled patients and *PIK3CA* MT patients.
- pCR rate in breast and axilla (total pCR) as defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer staging system (Appendix 6) by local evaluation in all enrolled patients and *PIK3CA* MT patients.

#### 3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Tumor ORR, assessed by centrally assessed breast MRI via modified RECIST (Appendix 3) in *PIK3CA* WT patients
- pCR rate in breast and axilla (total pCR) by local evaluation in *PIK3CA* WT patients.

The following secondary outcome measures will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- Compare letrozole plus GDC-0032 with letrozole plus placebo in terms of ORR, as measured by modified RECIST criteria (Appendix 3) using the following methods:
    - Breast ultrasound
    - Clinical breast exam (i.e., palpation)
    - Mammography
- Central assessment of changes in Ki67 levels upon treatment with letrozole plus GDC-0032 versus letrozole plus placebo from baseline to Week 3; baseline to surgery; and Week 3 to surgery
- Compare the centrally assessed PEPI score upon treatment with letrozole plus GDC-0032 with letrozole plus placebo
- Evaluate the changes in enhancing tumor volume from baseline to surgery as measured by breast MRI
- Evaluate different definitions of pCR including the following: a) ypT0, ypN0, and b) yoT0/is, ypNX (breast pCR)

### 3.4.2 Safety Outcome Measures

The safety and tolerability of GDC-0032 will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE, v4.0
- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Serious adverse events

- Protocol-defined adverse events of special interest
- Clinically significant changes in vital signs and in clinical laboratory results during the adverse event reporting period (see Section 5.3.1)

### 3.4.3 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- HRQoL, including side-effects of therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems), and patient functioning as measured using the EORTC QLQ–C30 and the modified breast cancer module QLQ–BR23

### 3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- ORR, pCR rate, and PEPI scores according to the decrease in Ki67 after 2 weeks of letrozole plus GDC-0032 and letrozole plus placebo.
- Expression of biomarkers before, during, and after therapy. These include, but are not limited to, the following:
    - PI3K pathway aberrations
    - Gene signatures, including intrinsic subtyping and PI3K pathway activity
    - Hormone receptor expression levels
    - Protein and phospho-protein markers and combinations
    - Mutations within cancer-associated genes
    - Copy number alterations in cancer-related genes
    - Plasma-based protein biomarkers
    - ctDNA
- Compare the rates of BCS and conversion to BCS in letrozole plus GDC-0032 versus letrozole plus placebo
- The relationship between GDC-0032 concentration and tumor response and/or drug safety response
- Letrozole concentrations with and without administration of GDC-0032
- The relationship between pharmacogenetic differences in drug metabolizing enzymes and transporters and other patient-specific covariates with PK of GDC-0032 or letrozole and/or drug response
- Changes from baseline to surgery in the apparent diffusion coefficient (ADC), a marker of tumor cellularity derived from diffusion-weighted MRI
- Concordance of the different imaging modalities (MRI [volume, enhancement, diffusion metrics], ultrasound, mammography) in measuring tumor response

# 4. MATERIALS AND METHODS

## 4.1 PATIENTS

Patients for this study include postmenopausal patients with ER+/HER2- untreated, Stage I-III operable breast cancer. The size of the primary tumor should be ≥2 cm by MRI.

### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF) prior to any study-specific procedure
- Female patients
- Postmenopausal status and age ≥18 years. Postmenopausal status is defined as follows:
  - Age ≥ 60 years or
  - Age < 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within postmenopausal range by local laboratory assessment or
  - Prior bilateral oophorectomy (≥ 28 days prior to Day 1 of treatment)
- Histologically confirmed invasive breast carcinoma, with all of the following characteristics:
  - Primary tumor ≥ 2 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 ≥ 2 cm and designated as the "target" lesion for all subsequent tumor evaluations.
  - Stage I to operable Stage III breast cancer
  - Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms).
- ER-positive and HER2-negative breast cancer, as per local laboratory or regional definition
- Breast cancer eligible for primary surgery
- Tumor tissue from FFPE core biopsy of breast primary tumor that is confirmed as evaluable for *PIK3CA* mutation status by central histopathology laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Fasting glucose ≤125 mg/dL
- Adequate hematological, renal, and hepatic function, as follows:
  - Absolute neutrophil count ≥ 1500/μL
  - Platelets count ≥100,000/μL

  - Hemoglobin $\geq$ 9 g/dL
  - Serum bilirubin $\leq 1.5\times$ the upper limit of normal (ULN)
  - Patients with known Gilbert's disease who have serum bilirubin $\leq 3 \times$ ULN may be enrolled
- Aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase $\leq 1.5\times$ ULN
- Serum creatinine $\leq 1.5\times$ ULN or creatinine clearance $\geq$ 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation:

  $(140-\text{age})\times(\text{weight in kg})\times(0.85)$
  $72\times(\text{serum creatinine in mg/dL})$
- International normalized ratio (INR) $<1.5\times$ upper limit of normal (ULN) and activated partial thromboplastin time (aPTT) $<1.5\times$ ULN

  For patients requiring anticoagulation therapy with warfarin, a stable INR between 2–3 is required. If anticoagulation is required for a prosthetic heart valve, then INR should be between 2.5–3.5.
- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Ability and willingness to comply with study visits, treatment, testing, and to comply with the protocol, in the investigator's judgment

### 4.1.2 Exclusion Criteria

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

- Any prior treatment for primary invasive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Metastatic (Stage IV) breast cancer
- 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 sentinel lymph node biopsy prior to study treatment
- Type 1 or 2 diabetes requiring antihyperglycemic medication
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteric absorption
- History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis)
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF) $>$ 470 msec

- Clinically significant (i.e., active) cardiovascular disease, like uncontrolled hypertension, unstable angina, history of myocardial infarction, cardiac failure class II-IV (New York Heart Association, Appendix 5), or any other that in the judgment of the investigator could jeopardize patient safety or study outcomes
- 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
- Active infection requiring intravenous (IV) antibiotics
- Patients requiring any daily supplemental oxygen
- Clinically significant history of liver disease, including viral or other known hepatitis, current alcohol abuse, or cirrhosis
- Known human immunodeficiency virus (HIV) infection
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications
- Significant traumatic injury within 3 weeks prior to initiation of study treatment
- Major surgical procedure within 4 weeks prior to initiation of study treatment
- Inability to comply with study and follow-up procedures
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

### 4.2.1 Patient Randomization

After written informed consent has been obtained and eligibility has been established, the study site will obtain a patient's identification number and treatment assignment using a permuted block randomization algorithm via an interactive voice or web-based response system (IxRS).

### 4.2.2 Stratification

Patients will be randomized into one of the two treatment arms in a 1:1 ratio based on the following stratification factors:

- Tumor size (T1-2 vs. T3)
- Nodal status (cytologically positive vs. radiologically or cytologically negative). If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then fine needle aspiration (FNA) or core biopsy is required to confirm nodal status.

### 4.2.3 Blinding

Investigators and patients will be blinded to treatment assignment of GDC-0032 or placebo.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS following approval from the Medical Monitor. Treatment codes should not be broken except in emergency situations where unblinding is needed for treatment decisions. Effort should be made to contact the Medical Monitor before unblinding. Patient treatment assignment may be unblinded at the time the patient discontinues from the blinded treatment phase at the request of the treating physician by contacting the IxRS following approval from the Medical Monitor and stating the reason for unblinding. Unblinding during the study will result in the withdrawal of a patient from the study. For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected, suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. The PK assay group will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed and bioanalytical methodology to employ. However, the PK scientist does not have access to the PK assay results and therefore stays blinded until the PK assay results need to be interpreted and reported. Samples from patients assigned to the comparator arm will be analyzed for letrozole. However, GDC-0032 assay will be analyzed by request (i.e., to evaluate a possible error in dosing).

## 4.3 STUDY TREATMENT

### 4.3.1 Formulation, Packaging, and Handling

#### 4.3.1.1 GDC-0032 and Placebo

GDC-0032 Drug Substance and Drug Product are manufactured according to current Good Manufacturing Practice guidelines for use in the clinical studies. Each lot of

GDC-0032 for clinical studies is subjected to a series of quality control tests to confirm its identity, purity, potency, and quality.

GDC-0032 is provided for use in clinical studies as a white, film-coated, immediate-release tablet formulation of 3 mg strength. The tablet formulation consists of GDC-0032 active, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and Opadry 2 white film coating. All excipients used in the formulation are compendial (USP/NF/Ph. Eur/JP) grade with the exception of the film-coating. The film-coating consists of polyvinyl alcohol-part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc, and these ingredients are compendial.

Placebo tablets will be identical in shape and color to the 3-mg tablets of GDC-0032 and will be indistinguishable from the 3-mg tablets of GDC-0032. The ingredients in the placebo tablets are identical to those in the 3-mg tablets of GDC-0032, except for the absence of GDC-0032 active.

The GDC-0032 active and placebo tablets are packaged in high-density polyethylene bottles, are labeled for clinical use, and should not be stored above 25°C.

For further details, see the GDC-0032 Investigator's Brochure.

#### 4.3.1.2 Letrozole

Letrozole will be labeled according to regulatory requirements in each country, as well as in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and will be labeled for investigational use only. The Sponsor will provide letrozole free of charge to all study sites.

Refer to the letrozole (e.g., Femara®) Package Insert or summary of product characteristics (SmPC) for details on the formulation and storage of letrozole.

### 4.3.2 Dosage, Administration, and Compliance

#### 4.3.2.1 GDC-0032 and Placebo

Patients will receive an oral, daily dose of 6 mg GDC-0032 or placebo on a schedule of 5 days on/2 days off for a maximum of 16 weeks. Patients will take GDC-0032 at the same time of day ±2 hours, unless otherwise instructed. Patients will be instructed as to the number of tablets to take. Patients will be asked to record the time and date that they take each dose in a medication diary.

Unless otherwise instructed, GDC-0032 or placebo should be taken on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal).

If a patient misses a GDC-0032 or placebo dose or vomits up a tablet, she should be instructed to skip that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up. Patients will be instructed to bring their medication diary to

each study visit for assessment of compliance. Patients will also be instructed to bring all unused tablets to each study visit for GDC-0032 or placebo accountability.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

#### 4.3.2.2 Letrozole

Patients will receive an oral, daily dose of 2.5 mg letrozole for 16 weeks (or until time of surgery at the investigator's discretion). No dose modifications of letrozole are permitted. Any overdose or incorrect administration of letrozole should be noted on the letrozole Administration eCRF. Adverse events associated with an overdose or incorrect administration of letrozole 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 (letrozole and GDC-0032) will be provided by the Sponsor where required by local health authority regulations. The investigational site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) 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 GDC-0032

The Sponsor will offer post-trial access to the study drug (GDC-0032, letrozole, or other study interventions) 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 would not 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 untreated, postmenopausal ER+/HER2−, early stage, operable breast cancer
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for untreated, postmenopausal postmenopausal ER+/HER2−, early stage, operable breast cancer
- 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
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 7 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

GDC-0032 was metabolized primarily by CYP3A4 in HLM and appeared to be a weak time-dependent inhibitor of CYP3A4. Although in vitro induction studies in human hepatocytes suggested that GDC-0032 has low-to-moderate potential to induce CYP3A4, preliminary data from the Phase I study (PMT4979g) indicate that 9 mg of GDC-0032 daily for 2 weeks in patients had no apparent effect on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate). Therefore, GDC-0032 may be administered concomitantly with CYP3A4 substrates without the risk of a pharmacokinetic DDI.

Letrozole is mainly metabolized to a pharmacologically inactive carbinol metabolite by CYP2A6 and CYP3A4 in vivo. GDC-0032, which has the potential to induce CYP3A4 based on in vitro induction studies, was administered in combination with letrozole in the expansion phase of Study PMT4979g to assess their DDI potential. Preliminary data from 10 patients in this cohort indicated that steady state plasma concentrations of both letrozole and GDC-0032, following once daily administration of the combination (2.5 mg letrozole plus 6 or 9 mg GDC-0032), were similar to historical, single-agent data

suggesting lack of DDI between GDC-0032 and letrozole. These preliminary results suggest that GDC-0032 and letrozole combination may be administered without the risk of a pharmacokinetic DDI.

In vitro CYP inhibition studies in HLMs and induction studies in human hepatocytes suggested a low to moderate potential of GDC-0032 to perpetrate DDIs. A clinical DDI study with rifampin (CYP3A4 inducer) and itraconazole (CYP3A4 inhibitor), to understand the effect of CYP inhibitors or inducers on the pharmacokinetics of GDC-0032, is currently ongoing (Study GP28617).

### 4.4.2 Prohibited Therapy

Prohibited therapy is as follows:

- **Anti-cancer therapy:** No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy (other than letrozole permitted in this protocol) will be allowed.
- **Hormone replacement therapy**, **topical estrogens (including any intra-vaginal preparations), hormonal contraception, megestrol acetate, and selective estrogen-receptor modulators used with prophylactic intent**: If a patient is receiving these at the moment of registration, treatment should be discontinued prior to randomization.
- **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. Patients who develop osteopenia or osteoporosis in the follow-up period may receive bone-targeted therapy as per the clinician's discretion. Primary use of bisphosphonates as a prevention of bone metastasis or as a prevention of bone loss is prohibited.
- **Potent CYP3A4 inhibitors:** Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole and itraconazole) with GDC-0032 should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If a strong CYP3A4 inhibitor is co-administered with GDC-0032, patients should be closely monitored for adverse reactions.

## 4.5 STUDY ASSESSMENTS

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

### 4.5.1 Informed Consent Forms and Screening Log

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

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

### 4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases that are currently active or that were active within the previous 5 years, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 15 days prior to the screening visit.

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

### 4.5.3 Physical Examination

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems as well as weight and height (height is measured at the screening visit only). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examination may be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

### 4.5.4 Vital Signs

Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

### 4.5.5 Electrocardiograms

Triplicate electrocardiogram (ECG) recordings will be obtained at each specified timepoint (see the schedule of assessments in Appendix 1).

### 4.5.6 Distant Sites Tumor Assessment

Baseline distant sites tumor staging procedures should be performed in alignment with National Comprehensive Cancer Network (NCCN) or national guidelines, within 28 days prior to randomization.

As a reference, as per NCCN guidelines, staging procedures are based on clinical stage:

- 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.
- For Stage IIIB and Stage IIIC: bone scan and CT of chest, abdomen, and pelvis should be conducted for all patients.

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.

### 4.5.7 Tumor and Response Evaluations

All measurable disease must be documented at screening and reassessed at subsequent timepoints as outlined in Appendix 1. Responses based on clinical breast exam, breast ultrasound, and mammography will be investigator-assessed. Whenever possible, assessments should be performed by the same evaluator to ensure internal consistency across visits. Response via breast MRI will be centrally assessed, and all assessments will be based on modified RECIST criteria (see Appendix 3).

**Clinical Breast Examination:** Assessment of primary breast tumor and regional lymph nodes must be done by physical examination (palpation) during baseline evaluation, Weeks 1, 5, 9, 13 and 16 during the treatment phase, and prior to surgery. Breast tumor measurement by caliper (preferred) or rule 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.

**Mammogram:** Bilateral mammograms must be obtained at baseline within 28 days prior to enrollment and again prior to surgery. Mammographic tumor measurements are to be recorded in the eCRF.

**Breast Ultrasound:** Bilateral breast ultrasounds must be obtained at baseline within 28 days prior to enrollment. Investigator decision whether to perform unilateral or bilateral ultrasounds performed at Week 9 and prior to surgery (Week 16) may be unilateral or bilateral and per investigator discretion. If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then FNA or core biopsy is required. Sonographic tumor measurements are to be recorded in the eCRF. The tumor site may be marked with a radiopaque clip or marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy.

**Breast MRI:** Contrast-enhanced breast MRI scans will be mandatory for all study patients at baseline (within 28 days prior to enrollment) and prior to surgery (Week 16). MRI is optional at Week 9, but will be mandatory if a primary breast lesion is not evaluable by ultrasound, or if there are signs of disease progression on the Week 9 ultrasound (see Figure 6).

Breast MRI scans should not be acquired within 48 hours after biopsy, and the 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 as assessed by the central reading facility, the scan may be repeated, at least 48 hours after the first scan before the start of study treatment. Other MRI acquisition sequences, such as diffusion-weighted imaging, may be acquired during this study during the MRI scan visits for each patient. Additional MRI-derived metrics such as ADC value may provide additional insight into changes in tumor cellular composition.

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

### 4.5.8 Surgical Treatment Plan

The planned and actual surgical treatment (BCS or mastectomy) performed should be documented and reported in the eCRF. Patients should be reassessed after completion of neoadjuvant therapy and prior to surgery.

### 4.5.9 Surgical Specimen – Pathology

The co-primary endpoint of the study (pCR) will be as identified by local pathology review. Guidelines regarding pathology specimen preparation, labeling and review are outlined in the pathology manual.

### 4.5.10 Laboratory Assessments

The following assessments will be performed at the local laboratory. The frequency of assessments is provided in Appendix 1.

- Hematology (complete blood count, including red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with differential [neutrophils, eosinophils, basophils, lymphocytes, monocytes, and other cells]), and platelet count.
- Coagulation (INR and aPTT/PTT)
- Fasting serum chemistry (blood urea nitrogen [BUN], creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, ALT), performed following $\geq$10-hour fast

- Fasting lipid profile and amylase (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides, amylase, and lipase) performed following a $\geq$10 hour fast
- Fasting insulin and glucose
- Glycosylated hemoglobin ($HbA_{1c}$)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)

The following assessments will be performed at a central laboratory. Instruction manuals outlining sampling procedures, storage conditions, and shipment instructions and supply kits will be provided for all central laboratory assessments:

- Mandatory tumor tissue
- 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 *PIK3CA* mutation testing as well as for other protocol-mandated exploratory assessments at baseline, Day 15, and at surgery.
- Tumor tissue should be of good quality based on total and viable tumor content. Evaluation of the patient's tumor sample for adequate tumor tissue content by a central laboratory must occur prior to initiation of study treatment. A minimum of ten unstained slides from a prior diagnostic FFPE core biopsy would be required for enrollment eligibility purposes.

  Two formalin-fixed, paraffin-embedded core needle biopsies and one freshly frozen OCT core needle biopsy are required at baseline and Day 15 (Week 3).

  A formalin-fixed, paraffin-embedded tumor block from surgical resection (Weeks 17 – 18) is required. If a tumor block cannot be obtained for various reasons (e.g., the tumor tissue is not sufficient at surgical resection), the site should discuss with the central study team. In such cases, paraffin-embedded, unstained slides (a minimum of 20 and up to 40 unstained slides) from a surgical specimen are required at surgery (Weeks 17 – 18).

  The specimens will be used for confirmatory central laboratory assessment of *PIK3CA* mutation status, Ki67, PTEN, ER/PgR and HER2 expression. In addition, other exploratory assessments, including but not limited to, PI3K signaling pathways may be evaluated, including protein expression and molecular profiling studies such as NGS and gene-expression.
- Plasma samples for exploratory research on candidate biomarkers include, but are not limited, to the following: ctDNA and plasma protein biomarkers
- Blood for NGS (if approved by local regulatory authorities)
- Blood for pharmacogenomics (if approved by local regulatory authorities)
- PK assessment

Plasma samples will be collected to measure letrozole and GDC-0032 concentrations (see 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.

### 4.5.11 Assay Methods

#### 4.5.11.1 Mutational Analysis for *PIK3CA*

The *PIK3CA* mutation assay will be performed by a central laboratory.

Somatic mutations in the *PIK3CA* gene are found in approximately 35%–40% of ER-positive breast cancers and occur most commonly in Exons 9 and 20 in the codons encoding amino acids E542, E545, and H1047 (Saal et al. 2005 [52]). Real-time polymerase chain reaction (RT-PCR) assays that amplify exons that are commonly mutated in *PIK3CA* offer a sensitive and quantitative method to detect mutations from a tumor specimen. DNA will be extracted from tumor samples and subjected to allele-specific PCR assays that detect the WT allele, as well as to assays for nucleotide substitutions that include, but are not limited to, the following amino acid changes: R88Q, N345K, C420R, E542K, E545K/A/G/D, E546K/E/R/L, M1043I, H1047R/L/Y, H1049R. Following histopathological review, samples with $<$10% tumor content may not be evaluable for the *PIK3CA* assay. Samples will be run on cobas z480 analyzer, and *PIK3CA* mutation status (mutant or WT) will be made using appropriate cutoffs and automated software.

A designation of *PIK3CA* status unknown will be assigned to a sample wherein any one of the predefined mutations was not conclusively assessed.

#### 4.5.11.2 Pharmacodynamic Biomarker Assays in Tumor Tissues

Ki67 antigen is an important cell cycle-related nuclear protein that is expressed by proliferating cells in all phases of the active cell cycle (G1, S, G2, and M phase). As such, it is a useful marker of the proliferative state of a tumor. Ki67 protein levels will be determined by IHC through the use of standard techniques.

PI3K pathway, and other pro-survival, biomarkers will be tested in the fresh tumor biopsies by IHC, including, but not limited to, phospho-S6, phospho-AKT, phospho-4EBP1, and phospho-ERK. If tissue quantity permits, change in expression of pathway biomarkers will be measured by the RPPA using OCT fixed tissue. The basis of the technology is to immobilize small amounts of lysate from a tumor biopsy sample in serial dilution on a microarray slide. Multiple samples are thus arrayed on a slide and can be probed with antibodies that detect a particular phospho-epitope. Using this technology, we will profile approximately 80 key signaling nodes representing a number of pathways known to be dysregulated in cancer, including receptors in the HER family, multiple components of PI3K/mTor signaling, as well as key members of the RAS/MAP kinase pathway.

#### 4.5.11.3 Analysis of Phosphatase Tensin Homolog Expression

PTEN status will be examined by IHC using a protocol that has been validated for specificity using several available cell line controls at a central laboratory. Tumor specimen will be scored only if appropriate staining is observed in internal control stromal or normal (non-tumor) tissue elements.

#### 4.5.11.4 Confirmation of Estrogen Receptor, Progesterone Receptor, and HER2 Status

ER, PR, and HER2 status will be determined at a central laboratory according to the American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) guidelines.

#### 4.5.11.5 Circulating Tumor DNA Analysis

ctDNA will be extracted from plasma samples collected from patients and used for the detection of oncogenic mutations using appropriate technologies. The prevalence of the mutations measured at baseline and post-treatment may provide information on response or resistance to therapy.

#### 4.5.11.6 Messenger RNA Expression Profiling

In cases where there is sufficient archival tissue to isolate RNA, gene expression will be performed using gene expression assays conducted on the NanoString platform or equivalent. Analysis may include, but is not limited to, a panel of genes important for intrinsic subtyping, breast cancer biology and PI3K signaling. The goal will be to generate a database of expression status to examine whether there are gene expression patterns that are associated with clinical response to GDC-0032.

#### 4.5.11.7 Next Generation Sequencing

In cases where there is sufficient material to isolate DNA, NGS will be performed using NGS platforms, such as Illumina or equivalent. The goal will be to determine whether the percentage of genetic mutations are associated with clinical response to GDC-0032.

#### 4.5.11.8 Copy Number Analysis

The level of copy number alterations in cancer-related genes may be determined using DNA-based technologies, either cytogenetically using chromosomal in situ hybridization (ISH), using next-generation sequencing platforms or by RT-PCR-based or equivalent technologies. For cytogenetic assays, detection may be either fluorescence-based (fluorescence in situ hybridization assay) or chromogenic-based (chromogenic in situ hybridization). Increased copy number of PI3K pathways activating genes may provide information on response or resistance to therapy.

#### 4.5.11.9 Plasma Biomarker Analyses

Assays to assess the expression of soluble, systemic cytokines, and chemokines from the plasma of patients will be carried out using appropriate methodologies, such as enzyme-linked immunosorbent assay (ELISA)-based or mass spectrometry-based or equivalent technologies.

#### 4.5.11.10 Plasma Pharmacokinetic Samples

Plasma GDC-0032 and letrozole samples will be analyzed using a validated liquid chromatography tandem mass spectrometry.

After the plasma samples are analyzed, any remaining samples may be used for exploratory metabolite profiling and identification, ex vivo protein binding, and PK, or pharmacodynamic assay development purposes.

#### 4.5.11.11 Pharmacogenetic Polymorphism Assay

If approved by the local regulatory authority, gene mutations will be assayed using multiplex PCR, allele-specific PCR, direct sequencing, or other acceptable methods. Results may be correlated to population PK parameters or other clinical measures in order to better understand the impact of genetic variants on drug metabolism, exposure, adverse events, and/or response.

A sample will also be utilized as a source of normal DNA to determine whether sequence variants in the *PIK3CA* gene and in other relevant oncogenes in the tumor DNA are somatic mutations or single nucleotide polymorphisms.

#### 4.5.11.12 Electrocardiograms

Triplicate ECG recordings will be obtained at each specified timepoint (see the schedule of assessments in Appendix 1).

### 4.5.12 Patient-Reported Outcomes

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of GDC-0032. The PRO questionnaires, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

The EORTC QLQ-C30 and the Modified Breast Cancer module QLQ-BR23 questionnaires will be used to assess HRQoL, including side-effects of systemic therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems) and patient functioning during the neoadjuvant period (refer to schedule of assessments in Appendix 1 for a detailed description of timepoints) and post-surgery follow-up.

The EORTC QLQ-C30 is a widely used HRQoL measure in oncology trials with excellent psychometric properties demonstrating both reliability and validity. The measure consists of “five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale” with a recall period of “the past week” (Aaronson et al. 1993 [1]). Scale scores can be obtained for each of the multi-item scales, global health status/QoL scale, and six

single items by using a liner transformation for standardization of the calculated raw score.

The EORTC QLQ-BR23 breast cancer module was first validated for use in 1995, uses a recall period of “the past week,” and is intended for use across multiple treatment modalities (i.e., surgery, chemotherapy, radiotherapy, and hormonal treatment). As this trial will include patients in the neo-adjuvant setting, the last seven items of the original BR23 questionnaire, items numbered 47 – 53 that deal with symptoms and side effects not relevant to the population under study, will be removed. These seven items addressed symptoms experienced by metastatic breast cancer patients and those undergoing radiation. Therefore, in consultation with the EORTC, these items were deleted, as the validity of the measure would not be compromised by their removal. In addition, as “oral mucositis” and “skin problems” are key symptoms of this therapy not assessed by currently available tools, validated items from the EORTC item bank were added to assess the presence and bothersomeness of oral mucositis (2 items: sore mouth/tongue, difficulty swallowing) and skin problems (2 items). Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results. Scale scores can be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score.

The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. Patients must complete these instruments in the clinic (cannot be taken home) prior to any healthcare provider interactions (i.e., prior to administration of study drug and prior to any other study assessment) to ensure that the validity of the instruments are not compromised and to ensure that data quality meet regulatory requirements.

Refer to Appendix 4 for the EORTC QLQ-C30 and the modified QLQ-BR23.

### 4.5.13 Samples for Clinical Repository

All residual samples (or leftover biologic samples after protocol-defined studies are completed) obtained during the study (FFPE, fresh-frozen, plasma, etc.) will be stored in an academic central repository. The specimens in the study repository will be made available for future biomarker research towards further understanding of treatment with GDC-0032, of breast cancer, related diseases, and adverse events, and for the development of potential, associated diagnostic assays. The implementation of study repository specimens is governed by the Study Steering Committee, with guidance from a dedicated Translational Research Committee to ensure the appropriate use of the study specimens.

All biomarker specimens will be retained for new research related to this study and/or disease in accordance with the recommendations and approval of the Study Steering

Committee. Samples will be only destroyed if required by local laws relating to the collection, storage, and destruction of biological specimens.

Specimens will be stored up to 15 years or until they are exhausted. The storage period will be in accordance with the institutional review board/ethics committee (IRB/EC)-approved ICF and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

#### 4.5.13.1 Confidentiality

Patient medical information associated with biologic specimens is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from biologic specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using biologic specimens will be available in accordance with the effective Translational Reseach Committee policy on study data publication.

## 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

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.

### 4.6.2 Study Treatment Discontinuation

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

- Pregnancy

- Disease progression
- Unacceptable toxicity

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 Conditions for Terminating the Study

Both the Sponsor and the investigator reserve the right to terminate their participation in the study under the circumstances agreed upon in the site agreement. Should this be necessary, both parties will arrange the procedures on an individual basis after review and consultation. In terminating the study, the Sponsor and investigator will assure that adequate consideration is given to the protection of the patients' interest.

## 5. ASSESSMENT OF SAFETY

### 5.1 SAFETY PLAN

GDC-0032 is not approved and is currently in early clinical development. Thus, the entire safety profile is not known at this time. Human experience is currently limited. The following information is based on results from ongoing clinical studies. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events, and laboratory abnormalities (see Section 5.3.5.3), defined and graded according to NCI CTCAE v4.0. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistry and blood counts. All serious adverse events and non-serious adverse events of special interest will be reported in an expedited fashion, via fax to Austrian Breast and Colorectal Cancer Study Group (ABCSG) safety department and also captured in the electronic data capture (EDC) system. In addition, the Sponsor and the investigators will review and evaluate observed adverse events on a regular basis.

All adverse events will be recorded during the trial and for 30 days after the last dose of study treatment or until the end of study visit, whichever occurs later. Patients who have an ongoing study treatment-related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

All adverse events should be attributed by the investigator to study drug or to another clearly identified etiology by the investigator (see Table 10).

Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are outlined in the following sections.

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

### 5.1.1 Management of Specific Adverse Events of GDC-0032

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

Due to the approximately 40-hour half-life for GDC-0032, investigators should consider holding GDC-0032 for certain Grade 2 toxicities until the adverse event resolves to Grade ≤ 1 as discussed below (e.g., stomatitis/mucositis, colitis, rash, diarrhea, pneumonitis). Certain toxicities can occur within 1–2 weeks of holding or discontinuing GDC-0032 drug (e.g., pneumonitis, colitis, rash). In these cases, the adverse event eventually resolves. Investigators should follow management guidelines and dose modifications for toxicities as described below, including administration of topical or systemic corticosteroids as appropriate.

**Table 1 Overall Dose Modification Guideline for GDC–0032-Related Adverse Events**

| | GDC-0032 |
|---|---|
| Starting dose | 6 mg at 5 days on / 2 days off |
| First reduction | 3 mg at 5 days on / 2 days off |
| Second reduction | 3 mg at 3 days on / 4 days off [a] |

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

#### 5.1.1.1 Management of Hyperglycemia

Hyperglycemia has been observed in patients who received GDC-0032 in the single-agent Phase I study.

Patients with diabetes requiring daily anti-hyperglycemic medication or who have a fasting blood glucose level >125 mg/dL will be excluded from the study. $HbA_{1c}$ and fasting glucose levels will be monitored at baseline, and additional monitoring of fasting glucose levels during the study will be implemented, as outlined in the schedule of assessments. Patients should be instructed to report symptoms associated with hyperglycemia such as thirst, frequent urination, and blurred vision.

Metformin is the first antihyperglycemic medication of choice because of the lower risk of hypoglycemia with this agent. Because metformin in some patients may also cause diarrhea and not be well tolerated, other antihyperglycemic medications such as sulfonylureas (e.g., glimepiride, glipizide) can be used. Extra caution should be used

with other drugs such as sulfonylureas because of the increased risk for hypoglycemia with these agents. Consultation with an endocrinologist can be helpful in managing hyperglycemia.

Specific dose modification and management guidelines for hyperglycemia are provided in Table 2.

**Table 2 Dose Modification and Management Guidelines for Hyperglycemia (Based on Fasting Blood Glucose)**

| Grade | Dose Modification and Management Guidelines for Hyperglycemia (based on fasting blood glucose) |
|---|---|
| Grade 2 | Initiation of an anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring will be implemented.<br>Dosing with GDC-0032 may either be held or continued per investigator evaluation. |
| Grade 3 (asymptomatic) | GDC-0032 dosing will be suspended and the patient will be managed as per standard of care, including implementation of additional glucose monitoring and initiation of, or an increase in, the dose of an anti-hyperglycemic therapy (e.g., metformin).<br>If the hyperglycemic event does not improve to Grade ≤ 1 within 28 days, GDC-0032 will be permanently discontinued.<br>If the hyperglycemic event improves to Grade ≤ 1 within 28 days, GDC-0032 dosing may resume at one dose level lower, with approval by the Medical Monitor. |
| Grade 3 (symptomatic) [a], Grade 3 (requiring hospitalization), or Grade 4 | GDC-0032 dosing will be suspended, and the patient will be managed as per standard of care, including implementation of additional glucose monitoring and initiation of, or an increase in, the dose of anti-hyperglycemic therapy.<br>If the hyperglycemic event does not improve to Grade ≤ 1 within 28 days, GDC-0032 will be permanently discontinued.<br>If the hyperglycemic event improves to Grade ≤ 1 within 28 days, GDC-0032 dosing may resume at one dose level lower, with approval by the Medical Monitor. |

[a] For example, blurred vision, frequent urination, excessive thirst.

#### 5.1.1.2 Management of Pneumonitis

Patients who require any daily supplemental oxygen are not eligible for the study. Patients will be assessed for pulmonary signs and symptoms throughout the study. Management guidelines for patients with possible pneumonitis are listed in Table 3.

**Table 3 Dose Modification and Management Guidelines for Pneumonitis**

| Grade | Intervention | Investigations | GDC-0032 [a] Dose Adjustment |
|---|---|---|---|
| 1 | No specific therapy required. | CT scan. Consider PFTs [b] Repeat CT scan every 8 weeks until return to baseline. | No change. |
| 2 | Symptomatic only. Prescribe corticosteroids if cough is troublesome. | CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs and bronchoscopy. | Reduce dose until improvement to Grade ≤ 1; consider interruption if symptoms are troublesome.<br>Interrupt treatment as long as corticosteroids are being given.<br>Restart GDC-0032 at the same dose if clinical benefit evident. Consider restarting at reduced dose if recurrent event or per discussion with Medical Monitor.<br>Discontinue treatment if recovery to Grade ≤ 1 is not evident within 28 days. |
| 3 | Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated. | CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs. Bronchoscopy is recommended. | Interrupt treatment until improvement to Grade ≤ 1.<br>Restart therapy within 28 days at a reduced dose if clinical benefit is evident.<br>Interrupt treatment as long as corticosteroids are being given. |
| 4 | Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated. | CT scan. Repeat CT scan every 4 weeks until return to baseline. Consider PFTs. Bronchoscopy is recommended. | Discontinue treatment. |

Table modified from White et al. 2010 [65].

CT = computed tomography; PFT = pulmonary function test.

PFTs include tests for diffusion capacity for carbon monoxide and room air oxygen saturation at rest (pulse oximetry).

[a] Dose reductions per Section 5.1.1.

[b] PFTs may be useful to monitor the effect of interventions such as dose reduction/discontinuation and corticosteroids, in conjunction with imaging (White et al. 2010 [65]).

#### 5.1.1.3 Management of Rash

Rash and other dermatological events should be closely monitored, and patients with severe rash should be monitored for associated signs and symptoms such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. For severe rash, dosing of GDC-0032 should be interrupted, and patients should be treated with

supportive therapy per standard of care. Use of antihistamines, as well as topical or systemic corticosteroids, may be considered (see Table 4).

**Table 4 GDC-0032 Dose Modification and Management Guidelines for Rash**

| Grade of Rash | GDC-0032 |
|---|---|
| Grade 1 | Continue dosing at current dose and monitor for change in severity.<br>Consider prescribing topical corticosteroids [a] |
| Grade 2 | Consider holding GDC-0032 or reducing to the next lower dose if rash is troublesome.<br>Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]). |
| Grade 3 or 4 | Hold GDC-0032 until Grade ≤ 1.<br>Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]).<br>Consider dermatological consultation.<br>Consider obtaining photographs of rash if permitted by local regulations.<br>After rash improves to Grade ≤ 1, restart GDC-0032 at the next lower dose upon discussion with Medical Monitor, or permanently discontinue. |

AE = adverse event.

AE grading is based on NCI CTCAE, Version 4.0.

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

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

#### 5.1.1.4 Management of Gastrointestinal Toxicity

##### 5.1.1.4.1 Management of Diarrhea

Patients should be closely monitored for gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain, stomatitis, and changes in stool, including checking for blood in stool if clinically indicated). Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. Gastrointestinal symptoms should be managed per protocol guidelines and institutional standard of care. For example, prompt management of diarrhea with antidiarrheal medications should be implemented. Because of the approximately 40-hour half-life of GDC-0032, investigators should hold GDC-0032 for Grade ≥ 2 diarrhea until it improves to Grade ≤ 1.

Specific dose modification and management guidelines for diarrhea are provided in Table 5.

## Table 5 GDC-0032 Dose Modification and Management Guidelines for Diarrhea

| Grade of Diarrhea | Dose Modification and Management Guidelines |
|---|---|
| Grade 1 | • Manage per institutional standard of care that includes antidiarrheals. [a] |
| Grade 2 | • Hold GDC-0032 and manage per institutional standard of care until Grade $\leq$ 1. These include antidiarrheals. [a]<br>• For persistent Grade 2 non-infectious diarrhea despite treatment with antidiarrheals, additional coadministration of corticosteroids (e.g., budesonide 9 mg PO QD) are recommended. [b] Non-infectious diarrhea can be diagnosed by stool culture.<br>• For persistent Grade 2 diarrhea lasting longer than 1 week with an adequate trial of anti-diarrheal medications, or for recurrent Grade 2 diarrhea, restarting at the next lower dose level should be strongly considered after diarrhea improves to Grade $\leq$ 1.<br>• If Grade 2 diarrhea is persistent despite treatment with SOC, consider work-up for colitis (e.g., performing abdominal/pelvis CT and/or endoscopy, and stool culture as appropriate). |
| Grade 3 or 4 | • Hold GDC-0032 and manage per institutional standard of care until Grade $\leq$1. These include antidiarrheals. [a]<br>• Consider work-up for colitis (e.g., performing abdominal/pelvis CT and/or endoscopy, and stool culture as appropriate).<br>• Restart GDC-0032 at the next lower dose level upon resolution to Grade$\leq$1.<br>• For persistent Grade 3$-$4 non-infectious diarrhea despite treatment with antidiarrheals, administration of systemic corticosteroids should be considered. [b]<br>• For Grade 3 diarrhea, may consider restarting at the same dose if event occurred because of lack of optimal medical management with antidiarrheal medications, after discussion with and approval by the medical monitor.<br>• For Grade 4 diarrhea, consider permanent discontinuation of GDC-0032. |

CT = computed tomography; PO = oral; QD = once daily; SOC = standard of care.

[a] Suggested antidiarrheals include the following: loperamide (initial: 4 mg, followed by 2 mg after each loose stool, up to 16 mg/day); diphenoxylate and atropine (Diphenoxylate 5 mg 4 times/day until control achieved [maximum: 20 mg/day], then reduce dose as needed; some patients may be controlled on doses of 5 mg/day; tincture of opium (6 mg of undiluted opium tincture [10 mg/mL]) 4 times daily.

[b] Examples of corticosteroid regimens include the following: For the steroid taper, suggested steroids include a methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg $\times$ 2 days, 40 mg $\times$ 2 days, 20 mg $\times$ 2 days, etc.). Can also consider budesonide 9 mg PO QD or prednisone 5 mg to 10 mg PO QD.

#### 5.1.1.4.2 Management of Colitis

Data as of October 2013 show an incidence rate for colitis of 6.2% (10/160) (1 at 16 mg; 8 at 9 mg; 1 at 6 mg + fulvestrant) with onset at approximately 100 days or longer after initiation of treatment with daily GDC-0032 dosing. Some patients have developed Grade 2 or Grade 3 diarrhea, which is non-responsive to anti-diarrheal medication. In some of these patients, a CT scan or colonoscopy has revealed colitis, which has resolved upon treatment with systemic corticosteroids.

For persistent Grade 2 diarrhea that does not resolve or for Grade $\geq$ 3 diarrhea, further evaluation should include colitis in the differential diagnosis with the appropriate work-up (e.g., abdominal/ pelvis CT scan, endoscopy with biopsy, stool cultures for cytomegalovirus, Clostridium difficile, and parasites). Grade $\geq$ 2 colitis should be managed by interruption of study treatment. In addition, discontinuation of nonsteroidal anti-inflammatory medications or any other medications known to exacerbate colitis symptoms should be considered. If noninfectious colitis is suspected, treatment with corticosteroids per institutional standard of care should be considered. It is suggested that prednisone (for oral administration) or solumedrol (for IV administration) are the corticosteroids of choice in the treatment of colitis. For severe symptoms, prednisone 60 mg or equivalent may be required to control initial symptoms, and the dose should be gradually tapered. Lower doses of prednisone, oral budesonide, or mesalamine (or other 5-aminosalicyclic acid derivatives) may be considered for less severe cases of colitis.

Specific dose modification and management guidelines for colitis are provided in Table 6.

**Table 6 GDC-0032 Dose Modification and Management Guidelines for Colitis**

| Grade of Colitis | Dose Modification and Management Guidelines |
|---|---|
| Grade 2 or Grade 3 (first event) | • Hold GDC-0032 and manage per institutional standard of care until Grade ≤ 1.<br>• Initiate corticosteroid therapy for noninfectious colitis. [a]<br>• Recommend discontinuation of any nonsteroidal anti-inflammatory medications or any other medications known to exacerbate colitis symptoms.<br>• Restart GDC-0032 at the next lower dose level upon resolution to Grade ≤ 1. In cases where risk/benefit is deemed favorable, may consider restarting at the same dose after discussion with and approval by the Medical Monitor. |
| Grade 3 (first recurrence) | • Hold GDC-0032.<br>• Initiate corticosteroid therapy for noninfectious colitis. [a]<br>• Permanently discontinue GDC-0032. In cases where risk/benefit is deemed favorable, may consider restarting at the next lower dose level upon resolution to Grade ≤ 1 after discussion with and approval by the Medical Monitor. |
| Grade 3 (second recurrence) or Grade 4 | • Permanently discontinue GDC-0032.<br>• Initiate corticosteroid therapy for noninfectious colitis. [a] |

[a] Examples of corticosteroid regimens include the following: For the steroid taper, suggested steroids include methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg × 2 days, 40 mg × 2 days, 20 mg × 2 days, etc.).

#### 5.1.1.4.3 Management of Stomatitis and Oral Mucositis

Aggressive mouth care for oral mucositis and stomatitis with mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) may also be helpful in managing symptoms, and it is recommended that these are implemented with early signs of dry mouth, Grade 1 mucositis, or Grade 1 stomatitis (see Table 7). Avoidance of spicy foods may also be helpful.

**Table 7 GDC-0032 Dose Delay and Modification Guidelines for Stomatitis and Oral Mucositis**

| Grade of Stomatitis/Mucositis | GDC-0032 |
|---|---|
| All grades | • Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics)<br>• Diet management (e.g., avoidance of spicy foods) |
| Grade 1 | • Monitor symptoms and initiate management (see above). Re-evaluate within 48 – 72 hours. |
| Grade 2 | • Hold GDC-0032 and manage until Grade ≤ 1.<br>• Restart GDC-0032 at the same dose.<br>• If Grade 2 stomatitis/oral mucositis recurs, hold GDC-0032 until Grade ≤ 1. Restart GDC-0032 at the next lower dose. |
| Grade 3 or 4 | • Hold GDC-0032 and manage until Grade ≤ 1. Restart GDC-0032 at the next lower dose.<br>• For Grade 3 event that was not adequately managed upon initial presentation, consider restarting at same dose upon discussion with Medical Monitor.<br>• For Grade 4 event, consider permanent discontinuation of GDC-0032. |

### 5.1.2 Management of Other Clinically Significant Adverse Events

See Table 8 for the dose modifications for other clinically significant adverse events.

**Table 8 GDC-0032 Dose Delay and Modification Guidelines for Other Clinically Significant Adverse Events**

| Grade | GDC-0032 |
|---|---|
| Grade 3: first event | • Hold GDC-0032 until Grade ≤ 1.<br>• Consider restarting at next lower dose. |
| Grade 3: recurrent<br>Grade 4: non-life-threatening | • Hold GDC-0032 until Grade ≤ 1.<br>• Restart at next lower dose. |
| Grade 4: life-threatening | • Permanently discontinue GDC-0032. |

### 5.1.3 General Guidance for Dose Modifications and Delays for Letrozole

The letrozole dose level cannot be modified. In general, the investigator can consider continuing letrozole if it is not thought to be letrozole-related.

All dose modifications should be based on the adverse event requiring the greatest modification and should be properly documented in the source documents.

### 5.1.4 Management of Increases in QT Interval

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

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

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

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

In rare circumstances, it may be acceptable to resume study drug, at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

### 5.1.5 Safety Monitoring for Letrozole

Letrozole is a nonsteroidal AI indicated for first line treatment of hormone receptor positive, locally advanced, or metastatic breast cancer in postmenopausal women. Letrozole is also indicated for adjuvant treatment in postmenopausal hormone-receptor positive patients and for the treatment of advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

The most frequently reported adverse events in a first line, breast cancer clinical trial with letrozole were bone pain, hot flushes, back pain, nausea, arthralgia, and dyspnea. Clinically significant adverse events also include bone effects (osteoporosis and bone fractures) and hypercholesterolemia. Discontinuations for adverse events other than progression of tumor occurred in 2% of patients on letrozole. Refer to the U.S. letrozole Package Insert or SmPC for additional information.

There are no expected significant overlapping toxicities between letrozole and GDC-0032. Routine safety monitoring and periodic laboratory tests for the letrozole and GDC-0032 combination will occur throughout the study.

## 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; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and 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 ABCSG)

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

- Fatal (i.e., the adverse event actually causes or leads to death)
- 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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 (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 ABCSG safety department 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 ABCSG)

Non-serious adverse events of special interest are required to be reported by the investigator to ABCSG safety department 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:

- Grade 4 hyperglycemia
- Grade $\geq$ 3 symptomatic hyperglycemia
- Grade $\geq$ 2 colitis or enterocolitis
- Grade $\geq$ 3 diarrhea
- Grade $\geq$ 3 rash
- Grade $\geq$ 2 pneumonitis

- 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 5.3.5.5)
- Suspected transmission of an infectious agent by the study drug

## 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 additionally reported to ABCSG safety department in case they fulfill the criteria for expedited reported in accordance with instructions provided in this section and in Section 5.4 –Section 5.6.

For each adverse event recorded on the Adverse Event CRF, 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

**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 until the end of study visit, whichever occurs later. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern deemed related to prior study drug treatment or study procedures (Section 5.6).

### 5.3.2 Eliciting Adverse Event Information

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

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

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

### 5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 4.0) will be used for assessing adverse event severity. Table 9 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 9 Adverse Event Severity Grading Scale**

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

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

Note: Based on the most recent version of NCI CTCAE (v 4.0), 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 one's self, 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 10):

- 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 (where 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 10 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 | Adverse events will be considered related, unless they fulfill the criteria as specified below.<br>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.

If known, a diagnosis 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.

#### 5.3.5.1 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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.

#### 5.3.5.2 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. The progression (increase and decrease) of an adverse event must be documented in the Adverse Event eCRF.

The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

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

#### 5.3.5.3 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:

- 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
- Clinically significant in the investigator's judgment

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 the 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

#### 5.3.5.4 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:

- 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
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

#### 5.3.5.5 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × 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 ABCSG safety department immediately (i.e., no more than 24 hours after learning of the event), either as serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

#### 5.3.5.6 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 ABCSG safety department (see Section 5.4.2). This includes death attributed to progression of breast cancer.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term “sudden death” should only be used 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 of 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.

#### 5.3.5.7 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 CRF.

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”).

#### 5.3.5.8 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:

- Perform an efficacy measurement for the study
- Hospitalization for respite care
- Planned hospitalization required by the protocol for breast cancer surgery
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
    - The patient has not suffered an adverse event
- Hospitalization due solely to progression of the underlying cancer
- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care
- Hospitalization for protocol mandated biopsies

#### 5.3.5.9 Adverse Events Associated with an Overdose

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 serious criteria, the event should be reported to the ABCSG safety department immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

#### 5.3.5.10 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO ABCSG

Certain events require immediate reporting to allow ABCSG safety department to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to ABCSG safety department 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 ABCSG safety department 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 ABCSG safety department 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

#### U.S. Medical Monitor Contact Information

Genentech's Medical Monitor Contact Information:

Medical Monitor: [redacted], M.D., Ph.D.

Telephone No.

Alternate Telephone No.: [redacted]

#### Medical Monitor Contact Information for Sites outside the United States:

Please refer to the country/region-specific phone numbers provided in the study binder.

### 5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the paper Serious Adverse Event reporting form and transmit to ABCSG safety department via fax. In addition the serious adverse event and non-serious adverse event of special interest information will be captured in the EDC system.

| | |
|---|---|
| Worldwide Sites: | ABCSG safety department |
| Fax No.: | +43 1 409 09 90 |

Relevant follow-up information should be submitted to ABCSG safety department as soon as it becomes available and/or upon request.

## 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 (SDV). For follow-up reports of serious adverse events and non-serious adverse events of special interest, investigators should record all follow up information immediately (i.e., within 24 hours) on the paper Serious Adverse Event reporting form and transmit to ABCSG safety department via fax. In addition the serious adverse event and non-serious adverse event of special interest follow-up information will be captured in the EDC system. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF and paper Serious Adverse Event form, if applicable.

All pregnancies reported during the study should be followed until pregnancy outcome, and they should be reported according to the instructions provided in Section 5.4.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor and/or ABCSG safety department 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

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should report these events directly to Genentech Safety Risk Management via telephone at 1-888-835-2555.

## 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:

- GDC-0032 Investigator's Brochure
- Local prescribing information for letrozole SmPC

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.

An IDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Primary and secondary efficacy analyses will include all patients who were included in the randomization. Final analysis will be performed after last patient, last visit (LPLV) and subsequent data cleaning, with patients allocated to the treatment arm associated by randomization.

Safety analyses will include all patients who were included in the randomization and received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

## 6.1 DETERMINATION OF SAMPLE SIZE

This study is designed for testing the effect of GDC-0032 on the two co-primary endpoints in all enrolled patients and in the *PIK3CA* MT patients and plans to enroll 330 patients in total. Assuming the *PIK3CA* mutation status will not be available (unknown) for approximately 10% of the patients and the prevalence of *PIK3CA* mutant is 40%, there will be approximately 120 patients in the *PIK3CA* MT cohort.

Given that the *PIK3CA* mutation status is not a stratification factor for randomization, there might be a possible imbalance between treatment arms within the *PIK3CA* MT cohort, which may reduce the statistical power in this cohort. To ensure the study provides sufficient statistical power even when the treatment assignment is imbalanced, the sample size was calculated based on a conservative scenario by assuming that the treatment assignment imbalance in *PIK3CA* MT is 40% vs. 60%. The sample size was calculated based on a chi²-test using continuity correction (Ury and Fleiss 1980 [63]).

To control an overall, two-sided, family-wise error rate under 20%, we use a two-sided significance level of 16% and 4% for the co-primary endpoints MRI ORR, and pCR, respectively.

Assuming 10% of the patients are unevaluable for the MRI ORR, approximately 300 enrolled patients and 108 patients in the *PIK3CA* MT cohort will be evaluable for analyses. This sample size allows us to detect an absolute percentage increase of 24% in MRI ORR rate in the GDC-0032 plus letrozole arm (64%) versus the letrozole-only arm (40%; Smith et al. 2005 [59]; Ellis and Ma 2007 [21]) in the *PIK3CA* MT cohort at 80% power and 16% two-sided significance level. The minimal detectable difference for ORR is approximately 15%.

Assuming that all patients are evaluable for pCR (i.e., approximately 330 enrolled patients and 120 in the *PIK3CA* MT cohort), this sample size provides 80% power to detect an absolute percentage increase of 18% in pCR in the GDC-0032 plus letrozole arm (19%) versus the letrozole-only arm (1%, Smith et al. 2005 [59]; Ellis and Ma 2007 [21]) in the *PIK3CA* MT cohort at the 4% two-sided significance level. The minimal detectable difference for pCR rate is approximately 13%.

If the prevalence of the *PIK3CA* mutation is lower than assumed, if there is more substantial treatment assignment imbalance in the *PIK3CA* MT cohort than assumed, or there is an increased number of unevaluable patients for the MRI ORR, the sample size may be increased to obtain the level of power at 80%, and the enrollment may be limited to patients with *PIK3CA* MT.

## 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 incidence of study treatment discontinuation for reasons other than disease progression will be tabulated.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables, stratification factors, and other baseline characteristics will be summarized by treatment arm.

## 6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include the ITT population; that is, all randomized patients will be included in the analyses, with patients grouped according to the treatment assigned at randomization.

### 6.4.1 Primary Efficacy Endpoint

The co-primary efficacy endpoints are (1) tumor ORR, assessed by modified RECIST criteria by breast MRI and (2) the rate of pCR in breast and axilla (total pCR) after completion of study drug.

The tumor ORR will be calculated by treatment arm in all enrolled population and in *PIK3CA* MT population. Within each population, the ORR for the two treatment arms will be compared at a two-sided alpha of 16% using a Cochran Mantel-Haenszel test, stratified by tumor size and nodal status. The pCR rate will also be calculated and compared at a two-sided alpha of 4% based on the same analytical approach as ORR. The two alpha values account for a family-wise type I error rate of 20%. Patients with early study termination and hence missing efficacy outcome will be considered as non-responders.

### 6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are as follows:

- Tumor ORR after completion of study treatment, assessed by modified RECIST criteria by breast MRI in *PIK3CA* WT patients.
- Rate of pCR in breast and axilla (total pCR) after completion of study drug in *PIK3CA* WT patients.

These endpoint measures will be summarized by treatment arm and will be analyzed analogue to the primary efficacy endpoint.

The following secondary efficacy endpoints will be performed in all enrolled patients and separated by *PIK3CA* mutation status:

- ORR by clinical breast examination, mammography, and breast ultrasound
- Ki67 values at baseline, Week 3, and surgery (centrally assessed)
- Change in Ki67 from baseline to Week 3; baseline to surgery, and Week 3 to surgery (centrally assessed)
- PEPI score (centrally assessed)
- Change in enhancing tumor volume from baseline to surgery as measured by breast MRI

- Evaluation of different definitions of pCR including the following: a) ypT0, ypN0, and b) ypT0/is, ypNX (breast pCR)

These endpoint measures will be summarized by treatment arm and will be compared between the two treatment arms within each population based on appropriate statistical analyses: ORR will be compared using a Cochrane Mantel-Haenszel test, stratified by tumor size and nodal status; PEPI, Ki67, and tumor volume change will be compared by regression analyses, adjusted for tumor size and nodal status. All secondary endpoints will be tested at a two-sided type I error of 5%.

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

## 6.5 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, and letrozole and GDC-0032 exposure.

Verbatim descriptions of adverse events will be mapped to thesaurus terms. Adverse event data will be listed by study site, treatment arm, patient number, and study day, severity, relationship to study drug, outcome, and action taken with the study treatments. Events occurring on or after treatment on Day 1 of Week 1 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 and vital sign (heart rate, blood pressure, and temperature) data will be displayed by time, with NCI CTCAE v4.0 Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized in tables by NCI CTCAE v4.0 grade.

## 6.6 PHARMACODYNAMIC ANALYSES

Ki67 biomarker analyses will include patients with at least one predose and one postdose biomarker assessment, with patients grouped according to the treatment actually received.

## 6.7 PHARMACOKINETIC ANALYSES

Individual $C_{max}$ and trough plasma concentrations ($C_{min}$) of GDC-0032 and letrozole from all patients enrolled will be reported. Mean of trough plasma concentrations of GDC-0032 and letrozole will be tabulated. The population pharmacokinetics of letrozole and GDC-0032 in this study will be compared with historical single-agent pharmacokinetics to assess the potential DDI between GDC-0032 and letrozole in this population.

Additional PK analyses on metabolites of GDC-0032, letrozole, and/or other concomitant medications may be conducted as appropriate.

## 6.8 PATIENT-REPORTED OUTCOME ANALYSES

Patient-reported outcomes of breast cancer symptoms, patient functioning, and HRQoL will be assessed by the EORTC QLQ-C30 and the modified Breast Cancer module (QLQ-BR23)

Summary statistics (mean, standard deviation, median and range) of linear transformed scores will be reported for all the items and subscales of the EORTC QLQ-C30 questionnaire, and the modified QLQ-BR23 according to the EORTC scoring manual guidelines for each assessment time point. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) of items and subscales over time will be provided for each treatment arm from the baseline assessment.

Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results.

Completion and compliance rates will be summarized at each timepoint by treatment arm with reasons for missing data. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses. The number and proportion of patients who improved, worsened, or remained stable for all of the symptom and functional domains, global QoL, and single items of the EORTC QLQ-C30 and QLQ-BR23 will be summarized.

## 6.9 EXPLORATORY ANALYSES

Additional details on analyses will be specified in the SAP.

## 6.10 INTERIM ANALYSES

The IDMC will conduct interim analyses to review the unblinded safety data after the first 20 patients have either 1) finished the 30-day, follow-up visit after the surgery, or 2) been on study for 20 weeks after the randomization date (for those who do not receive the surgery). All available information of all enrolled patients with all available assessments at the respective timepoint will be included in the interim analyses. In addition, the IDMC or the Medical Monitor may request additional ad hoc meetings of the IDMC at any time during the study to review safety data.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

ABCSG will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, ABCSG and/or all involved clinical research associates (CRAs) will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

ABCSG will produce a Data Management Plan that describes the quality checking to be performed on the data. The Sponsor will perform oversight of the data management of this study, including review of the ABCSG's data management plan and corresponding specifications. Data will be transferred electronically from ABCSG to the Sponsor at the end of the study and whenever otherwise contractually agreed, and the Sponsor's standard procedures will be used 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 at ABCSG and records retention for the study data will be consistent with the ABCSG's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff. Original PRO questionnaires will be kept in the patient's medical record as source documentation.

## 7.2 DATA(BASE) MANAGEMENT

ABCSG Clinical Data Management will check all e-forms for plausibility and consistency by automatic edit checks and manual data review according to study-specific data management plan (DMP). If necessary, web-based data queries (data clarification requests [DCRs]) will be generated and subsequently visible for the investigators, dedicated site staff, responsible CRAs, and responsible ABCSG staff. For those eCRFs which pass all verification procedures and are regarded as correct and complete, they will be frozen subsequently by ABCSG clinical data management. Consequently, no further data entries or changes on frozen eCRFs are possible. The status of frozen eCRFs is flagged by the specific icon.

Clinical Data Management ensures that the database is corrected for the following eCRF issues without immediate notification to site staff (self-evident corrections). Notification of site staff is provided via a specific report after final data cleaning procedures and before final data confirmation by the investigator or a designee:

- misspellings/typing errors that do not change the meaning of the word
- location of data recorded at an incorrect variable field or eForm (e.g., moving lab data from general comments to the appropriate lab table)

- standard time to 24-hour clock
- correction of date format, if required (dd/mm/yyyy)
- if equivalent units of terms are recorded instead of the acceptable ABCSG standard
- data changes due to plausibility checks and eCRF content (e.g., combination of several variables and/or eCRFs)

All data management workflows are described in detail in the relevant SOPs and working instructions of ABCSG.

## 7.3 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using the Clinical Data Management System "MACRO," a web-interface DATAPORT. Sites will receive training by the responsible CRAs and have access to a manual for appropriate eCRF completion (web data entry).

All eCRFs should be completed by designated, trained site staff in a timely manner, usually within 2 weeks after the patient visit. Electronic CRFs should be reviewed and respective data confirmation eCRF should be electronically signed and dated by the investigator or a designee at the end of the study.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a storage medium (compact disc [CD], digital video disk [DVD] etc.) that must be kept with the study records. Acknowledgement of receipt of the storage medium is required.

## 7.4 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

## 7.5 USE OF COMPUTERIZED SYSTEMS

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

## 7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data (if applicable), ICFs, 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 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP 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/European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

## 8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs) 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 ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved consent forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. 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 separate, specific 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 provide a separate signature.

**The ICFs must be signed and dated by the patient or the patient's legally authorized representative before participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.** The eCRF contains a section to document whether the patient has signed the ICF or not.

The ICFs 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.

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the patients are

completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs 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 ICF 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.

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the sponsor, the affiliated groups, or contract research organizations (CROs) according to the applicable local laws and regulations, if applicable 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 Sponsor, affiliated groups, or CROs are 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 local IRB/EC. The Sponsor, affiliated groups, or CROs 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 local health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 8.4 DATA PRIVACY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique 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 only be disclosed to third parties as permitted by the ICF (or separate authorization for use and

disclosure of personal health information) signed by the patient, unless permitted or required by local 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, provided the patient has given consent.

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. The patient will have to consent to such access by signing the informed consent form.

## 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (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, ICFs, and documentation of IRB/EC and governmental (health authorities) approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

## 9.2 ON SITE QUALITY CONTROL (MONITORING)

During the study, CRAs will visit their respective sites on a regular basis as outlined in the study specific monitoring plan (MP) and all other relevant specifications, in order to guarantee adherence to the protocol and to the principles of GCP and to check for the progress of enrolment, adequate storage conditions of IMP and adequate drug dispensing and accounting records.

CRAs will review documented data in the eCRFs for completeness and accuracy according to the study-specific MP, subsequently flag all reviewed pages with a specific mark ("SDV done") within the EDC system "MACRO," web-interface DATAPORT, developed by [redacted]. The CRAs will raise data queries ("DCRs") in cases of missing source data or incorrect data entries. Immediately after electronic issue of the queries, they become visible to the investigator, the clinical data managers, and the ABCSG clinical safety officers ("raised DCRs"). CRAs and/or clinical data managers

and/or ABCSG clinical safety officers will follow up with trial site personnel until final data query resolution.

## 9.3 PROTOCOL DEVIATIONS

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

## 9.4 SITE INSPECTIONS

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

## 9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech and will be managed by Genentech in collaboration with the Breast International Group (BIG), ABCSG, and the Spanish Breast Cancer Research Group (SOLTI). Genentech in collaboration with BIG, ABCSG, and SOLTI will provide clinical operations management, data management, and medical monitoring. Approximately 110 U.S. and international sites will participate to enroll approximately 330 patients.

An IDMC will be in place throughout the study and will provide oversight of safety and efficacy analyses (see Section 3.1.2).

After written informed consent has been obtained, the study site will obtain the patient's screening number from the IxRS system. Once eligibility has been established, the patient will be enrolled, and the study site will obtain the patient's identification number from the IxRS. Once results of the tissue analysis are made available, the patient will be randomized, and the site will obtain the blinded treatment assignment from the IxRS. The IxRS will manage GDC-0032/placebo drug inventory at all sites and letrozole drug inventory at all study sites outside the United States. IxRS will be required to randomize patients, to monitor enrollment and patient status, and to manage study treatment requests and shipments.

Patient data will be recorded via an electronic data capture (EDC) system from [redacted] ([redacted], United Kingdom), which will be managed by ABCSG using eCRFs (see Section 7.2).

Central laboratories, including Genentech and Genentech collaborators, will be used for *PIK3CA* mutation detection, Ki67, and PTEN status and/or will provide kits for PK, pharmacogenomic, tissue, whole blood, and plasma sample analyses to be conducted at central laboratories, Genentech, or Genentech collaborators.

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

## 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

| Study procedures | Screening | Treatment Phase | | | | | | Surgery [a,f] | Post Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | W9 | W13 | W16 (Presurgical Visit) | W17 – W18 (Surgery) | 4 Weeks (+1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | 57 (±2) | 85 (±2) | 106 – 112 | 113 – 126 | |
| Informed consent [a] | x | | | | | | | | |
| Medical history and demographic data [b] | x | | | | | | | | |
| Physical examination [c] | x | | | x | x | x | x | | x |
| Clinical breast and regional lymph node examination | x | x | | x | x | x | x | | |
| Vital signs [d] | x | x | x | x | x | x | x | | x |
| ECOG Performance Status | x | x | x | x | x | x | x | | x |
| 12-Lead ECG [e] | x | | x | | | | | | |
| Mammography | x | | | | | | x | | |
| Breast ultrasound and axillary lymph node status [f] | x | | | | x | | x | | |
| Breast MRI [g] | x | | | | | | x | | |
| Collection of tumor samples [h] | x | | x | | | | | x | |
| Confirmation of receipt of adequate tissue for *PIK3CA* assessment | x | | | | | | | | |
| CBC with differential and platelet count [i] | x | x | | x | x | x | x | | x |

# Appendix 1
# Schedule of Assessments (cont.)

| Study procedures | Screening | Treatment Phase | | | | | | Surgery [a,f] | Post Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | W9 | W13 | W16 (Presurgical Visit) | W17 – W18 (Surgery) | 4 Weeks (+1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | 57 (±2) | 85 (±2) | 106 – 112 | 113 – 126 | |
| Fasting serum chemistry [j] | x | x | | x | x | x | x | | x |
| Glycosylated hemoglobin ($Hb_{A1c}$) | x | | | | | | | | |
| Fasting insulin and glucose [k] | x | x | | x | x | x | x | | x |
| Fasting lipid profile and amylase [l] | x | | | x | | x | x | | x |
| Coagulation (INR and aPTT) | x | | | x | x | x | x | | x |
| Urinalysis (laboratory) [m] | x | | | x | x | | x | | x |
| Blood sample for plasma protein biomarkers [n] | | x | | | x | | x | | |
| Blood sample for ctDNA [o] | | x | | | x | | x | | |
| Blood sample for NGS [p] | | x | | | | | | | |
| Pharmacogenomic sample [q] | | x | | | | | | | |
| Concomitant medication [r] | x | x | x | x | x | x | x | | x |
| Adverse events | x | x | x | x | x | x | x | | x |
| Inclusion/exclusion criteria [s] | x | | | | | | | | |
| Visit with breast surgeon (may occur from Week 13) | | | | | | x | | | |
| Surgery [t] | | | | | | | | x | |
| Randomization | x | | | | | | | | |
| Letrozole accountability/dispensation | | x | x | x | x | x | x | | |

# Appendix 1
# Schedule of Assessments (cont.)

| Study procedures | Screening | Treatment Phase | | | | | | Surgery [a,g] | Post Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W3 | W5 | W9 | W13 | W16 (Presurgical Visit) | W17 – W18 (Surgery) | 4 Weeks (+1W) from Surgery |
| Days | -28 to -1 | 1 | 15 (+2) | 29 (±2) | 57 (±2) | 85 (±2) | 106 – 112 | 113 – 126 | |
| GDC-0032/placebo accountability/ dispensation | | x | x | x | x | x | x | | |
| Patient-reported outcomes [u] | | x | | x | x | x | x | | x |
| Pharmacokinetic sample (see Appendix 2) | | x | x | | x | | | | |

aPTT = activated partial thromboplastin time; CA-125 = cancer antigen 125; CTCs = circulating tumor cells; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; MRI = magnetic resonance imaging; NGS = next-generation sequencing.

Note: All assessments should be performed before dosing, unless otherwise stated. Some assessments may be performed outside the window indicated to accommodate holidays, unforeseen scheduling issues, or ongoing safety issues with the trial and the patient, after approval by the Medical Monitor.

[a] Perform within 28 days prior to Day 1 of Cycle 1. Signed informed consent must be provided prior to any study-specific evaluations. Assessments performed as standard of care within the timeframe may be used.

[b] Medical history includes clinically significant diseases that are currently active or that were active within the last 5 years, surgeries, cancer history (including date of diagnosis, primary tumor histology, grade, staging, prior cancer therapies, and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse. Demographic data include age, sex, and self-reported race/ethnicity.

[c] A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems as well as weight (in kilograms) and height (in centimeters; height is measured at the screening visit only). Perform symptom-directed physical examination after baseline assessment.

[d] Vital signs include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position and temperature. Oxygen saturation is obtained by pulse oximetry after the patient has been in a seated position for ≥ 5 minutes. Obtain vital signs predose.

[e] Triplicate ECG recordings will be obtained at each specified timepoint. A window of ± 30 minutes is acceptable for all timepoints. Submit all ECGs to the diagnostic facility for central review.

[f] Baseline evaluation of axillary lymph nodes assessed with ultrasound.

# Appendix 1
# Schedule of Assessments (cont.)

[g] MRI evaluation is optional at Week 9. MRI is mandatory at Week 9 in the event that disease progression is suspected, or if the primary lesion is not evaluable by ultrasound at baseline. Send all scans to the central reading facility for evaluation.

[h] Two formalin-fixed, paraffin-embedded core needle biopsies and one freshly frozen OCT core needle biopsy are required prior to initiation of treatment (pretreatment) and also on Day 15. A formalin-fixed, paraffin-embedded tumor block from a surgical resection is required at surgery (Weeks 17 – 18).

[i] Complete blood count includes red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[j] Fasting ($\geq$10-hour fast) serum chemistry: BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, serum bilirubin, alkaline phosphatase, glucose, AST, and ALT. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[k] Glucose levels may be obtained by fingerstick. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[l] Fasting lipid profile includes total cholesterol, HDL, LDL, triglycerides, amylase, and lipase. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[m] Includes specific gravity, pH, glucose, protein, ketones, and blood. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

[n] Pretreatment sample for plasma protein biomarkers should be obtained prior to dosing. Refer to laboratory manual for more information.

[o] Pretreatment sample for ctDNA may be obtained on Day 1 prior to dosing. This sample will also be collected prior to dosing at Week 9 and at Week 16. Refer to laboratory manual for more information.

[p] Blood for NGS will be collected if allowed by local regulatory authorities and may be obtained prior to dosing on Week 1.

[q] Blood for pharmacogenomics will be collected if allowed by local regulatory authorities and may be obtained prior to dosing on Week 1.

[r] Record all medications used by the patient within 15 days before screening (including prescription, over-the-counter, herbal remedies, and supplements).

[s] All of the study's inclusion criteria and none of the exclusion criteria should be met prior to study entry.

[t] Surgery will take place after at least 16 weeks of combination treatment (i.e., from Week 17 to Week 18), and generally no more than 2 days after the last dose of study medication.

[u] The PRO questionnaires (EORTC QLQ-C30, modified QLQ-BR23) will be completed by the patients at the investigational site. All PRO questionnaires must be administered prior to any other study assessment(s) and prior to administration of study drug.

# Appendix 2
# Schedule of Pharmacokinetic Assessments

| Visit | Timepoint | PK Assessments |
|---|---|---|
| Day 1 | 3 hours post (±60 min) letrozole and GDC-0032/placebo administration | Letrozole PK |
| | | GDC-0032 PK |
| Day 15 (+2 days) | 0 – 4 hours prior to letrozole and GDC-0032/placebo administration | Letrozole PK |
| | | GDC-0032 PK |
| | 3 hours (±60 min) post letrozole and GDC-0032/placebo administration<br>ECG before PK | Letrozole PK |
| | | GDC-0032 PK |
| Day 57 (+/– 2 days) | 3 hours post (±60 min) letrozole and GDC-0032/placebo administration | Letrozole PK<br>GDC-0032 PK |

ECG = electrocardiogram; min = minutes; PK = pharmacokinetics.

Record exact time of dose administration and sample collection.

# 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 therapy in early breast cancer. Ultrasound, mammography, and clinical exam are all

[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.

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

### 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

## 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.

**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
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures

## EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): _____

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

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

Please go on to the next page

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

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

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

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

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

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 31. Did you have a dry mouth? | 1 | 2 | 3 | 4 |
| 32. Did food and drink taste different than usual? | 1 | 2 | 3 | 4 |
| 33. Were your eyes painful, irritated or watery? | 1 | 2 | 3 | 4 |
| 34. Have you lost any hair? | 1 | 2 | 3 | 4 |
| 35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair? | 1 | 2 | 3 | 4 |
| 36. Did you feel ill or unwell? | 1 | 2 | 3 | 4 |
| 37. Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 38. Did you have headaches? | 1 | 2 | 3 | 4 |
| 39. Have you felt physically less attractive as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 40. Have you been feeling less feminine as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 41. Did you find it difficult to look at yourself naked? | 1 | 2 | 3 | 4 |
| 42. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 43. Were you worried about your health in the future? | 1 | 2 | 3 | 4 |
| 44. Have you had skin problems (e.g. itchy, dry)? | 1 | 2 | 3 | 4 |
| 45. Did itching of your skin bother you? | 1 | 2 | 3 | 4 |
| 46. Have you had a sore mouth or tongue? | 1 | 2 | 3 | 4 |
| 47. Have you had trouble swallowing? | 1 | 2 | 3 | 4 |

Please go on to the next page

# Appendix 4
# EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23 Measures (cont.)

| **During the past four weeks:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 48. To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 49. To what extent were you sexually active? (with or without intercourse) | 1 | 2 | 3 | 4 |
| 50. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |

# Appendix 5
# New York Heart Association Classifications

## Clinical Evaluation of Functional Capacity of Patients

| NYHA | Functional Class | Description | Objective Assessment |
|---|---|---|---|
| I | Mild | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea. | No objective evidence of cardiovascular disease. |
| II | Mild | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea | Objective evidence of minimal cardiovascular disease |
| III | Moderate | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea. | Objective evidence of moderately severe cardiovascular disease. |
| IV | Severe | Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. | Objective evidence of severe cardiovascular disease. |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors

## Tumor (T)

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ |
| Tis (DCIS) | DCIS |
| Tis (LCIS) | LCIS |
| Tis (Paget) | Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted. |
| T1 | Tumor ≤20 mm in greatest dimension |
| T1mi | Tumor ≤1 mm in greatest dimension |
| T1a | Tumor >1 mm but ≤5 mm in greatest dimension |
| T1b | Tumor >5 mm but ≤10 mm in greatest dimension |
| T1c | Tumor >10 mm but ≤20 mm in greatest dimension |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors (cont.)

## Tumor (T)

| | |
|---|---|
| T2 | Tumor >20 mm but ≤50 mm in greatest dimension |
| T3 | Tumor >50 mm in greatest dimension |
| T4 | Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)[a] |
| T4a | Extension to the chest wall, not including only pectoralis muscle adherence/invasion |
| T4b | Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma |
| T4c | Both T4a and T4b |
| T4d | Inflammatory carcinoma |

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DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

Note: The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cut-off for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cut-off. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

[a] Invasion of the dermis alone does not qualify as T4.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant Tumors (cont.)

## Regional Lymph Nodes (N)

| Clinical | |
|---|---|
| NX | Regional lymph nodes cannot be assessed (e.g., previously removed) |
| N0 | No regional lymph node metastases |
| N1 | Metastases to movable ipsilateral level I, II axillary lymph node(s) |
| N2 | Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted |
| | OR |
| | Metastases in clinically detected [a] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases |
| N2a | Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures |
| N2b | Metastases only in clinically detected [a] ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases |
| N3 | Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement |
| | OR |
| | Metastases in clinically detected [a] ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases |
| | OR |
| | Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement |
| N3a | Metastases in ipsilateral infraclavicular lymph node(s) |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Regional Lymph Nodes (N)

| | Clinical |
|---|---|
| N3b | Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s) |
| N3c | Metastases in ipsilateral supraclavicular lymph node(s) |

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[a] Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pNX | Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study) |
| pN0 | No regional lymph node metastasis identified histologically |
| Note: ITCs are defined as small clusters of cells ≤0.2 mm, or single tumor cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by IHC methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated. | |
| pN0(i–) | No regional lymph node metastases histologically, negative IHC |
| pN0(i+) | Malignant cells in regional lymph node(s) ≤0.2 mm (detected by H&E or IHC including ITC) |
| pN0(mol–) | No regional lymph node metastases histologically, negative molecular findings (RT-PCR) |
| pN0(mol+) | Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC |
| pN1 | Micrometastases |
| | OR |
| | Metastases in 1–3 axillary lymph nodes |
| | AND/OR |
| | Metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| pN1mi | Micrometastases (>0.2 mm and/or >200 cells but none >2 mm) |
| pN1a | Metastases in 1–3 axillary lymph nodes, at least one metastasis >2 mm |
| pN1b | Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pN1c | Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected |
| pN2 | Metastases in 4–9 axillary lymph nodes |
| | OR |
| | Metastases in clinically detected [a] internal mammary lymph nodes in the absence of axillary lymph node metastases |
| pN2a | Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit $>2$ mm) |
| pN2b | Metastases in clinically detected[d] internal mammary lymph nodes in the absence of axillary lymph node metastases |
| pN3 | Metastases in $\geq 10$ axillary lymph nodes |
| | OR |
| | Metastases in infraclavicular (level III axillary) lymph nodes |
| | OR |
| | Metastases in clinically detected[c] ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes |
| | OR |
| | Metastases in $>3$ axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| | OR |
| | Metastases in ipsilateral supraclavicular lymph nodes |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Pathologic (pN)[1]

| | |
|---|---|
| pN3a | Metastases in ≥ 10 axillary lymph nodes (at least 1 tumor deposit >2 mm) |
| | OR |
| | Metastases to the infraclavicular (level III axillary lymph) nodes. |
| pN3b | Metastases in clinically detected [b] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; |
| | OR |
| | Metastases in > 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected [a] |
| pN3c | Metastases in ipsilateral supraclavicular lymph nodes |
| **Post-treatment ypN** | |
| Post-treatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "SN" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by AND. | |
| The X classification will be used (ypNX) if no yp post-treatment SN or AND was performed | |
| N categories are the same as those used for pN | |

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

AND = axillary node dissection; H&E = hematoxylin and eosin stain; IHC = immunohistochemical; ITC = isolated tumor cells; RT-PCR = reverse transcriptase/polymerase chain reaction.

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[1] Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (SN) for "sentinel node," for example, pN0(SN).

[a] "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

[b] "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine-needle aspiration biopsy with cytologic examination.

## Distant Metastases (M)

| | |
|---|---|
| M0 | No clinical or radiographic evidence of distant metastases |
| cM0(i+) | No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other non-regional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases |
| M1 | Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm |

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**Post-treatment yp M classification.** The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pre-therapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.

# Appendix 6
# American Joint Committee on Cancer TNM Classification of Malignant (cont.)

## Anatomic Stage/Prognostic Groups[a]

| Stage | T | N | M[c] |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| IA | T1[c] | N0 | M0 |
| IB | T0 | N1mi | M0 |
| | T1[c] | N1mi | M0 |
| IIA | T0 | N1[b] | M0 |
| | T1[c] | N1[b] | M0 |
| | T2 | N0 | M0 |
| IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| IIIA | T0 | N2 | M0 |
| | T1[c] | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| IIIB | T4 | N0 | M0 |
| | T4 | N1 | M0 |

## Appendix 6
## American Joint Committee on Cancer TNM Classification of Malignant (cont.)

| Stage | T | N | Mc |
|---|---|---|---|
| | T4 | N2 | M0 |
| IIIC | Any T | N3 | M0 |
| IV | Any T | Any N | M1 |

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Note: Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy. Post-neoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0cM0.

[a] T1 includes T1mi.

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

[c] M0 includes M0(i+); The designation pM0 is not valid; any M0 should be clinical. If a patient presents with M1 prior to NAST, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.