COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL
200 FR. 4

(PHASE I ONLY)

Study Title: PMT4979 GO00886: An Open-Label, Phase I/II, Dose-Escalation Study Evaluating the Safety and Tolerability of GDC-0032 in Patients with Locally Advanced or Metastatic Solid Tumors or Non-Hodgkin's Lymphoma and in Combination with Endocrine Therapy in Patients with Locally Advanced or Metastatic Hormone Receptor-Positive Breast Cancer

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Funding Source: Genentech, Inc.

INVITATION TO PARTICIPATE AND DESCRIPTION OF PROJECT

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. This research study includes only subjects who choose to take part. Your participation is entirely voluntary. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You may also discuss it with your health care team. If you have any questions, you may ask your study doctor for more explanation. In this consent form, "you" refers to the subject.

Genentech, Inc., a member of the Roche group, is the sponsor of this research study. Genentech, the study sponsor, will pay the study center to cover the study center's costs of conducting this research study.

Please read the following consent form to learn about what will happen if you agree to take part in this research study. This consent form may contain some words that you do not understand. Please ask your study doctor or someone from the study staff to explain any words or information that you do not clearly understand.

After you are sure that you clearly understand the risks and benefits of taking part in this study, if you choose to take part in the study, you will be asked to sign this consent form. You should not sign this consent form if you have any questions that have not been answered. By signing this consent form, you are confirming that the study has been explained to you, and that you give your permission to be a part of the study.

PURPOSE

You are being asked to take part in this study because you have an advanced stage cancer and one or more of the following conditions:

- There is no proven therapy for your cancer
- Your cancer got worse while you were treated with standard therapy
- You had intolerable side effects when you were treated with standard therapy

The purpose of this study is to test the safety of an experimental drug (GDC-0032) to determine a safe and tolerated dose, how often it should be taken, how well patients with cancer can tolerate this experimental drug, and to measure how your body processes the study drug at different dose levels. We want to find out what effects, good and/or bad, it has on you and your cancer.

In animal studies and laboratory experiments, GDC-0032 inhibits a protein called PI3K (phosphoinositide 3 kinase) that helps cancer cells grow. This experimental drug has been shown to prevent or slow the growth of many different types of human cancer cells grown in animals.

The use of GDC-0032 in this research study is experimental, which means that it is not approved by the U.S. Food and Drug Administration (FDA) for cancer or any other disease. GDC 0032 has not been used in humans before.

Approximately 623-723 subjects will take part in this study at study centers in the United States and in Europe. The study is divided into two phases, Phase I and Phase II. If you are being asked to participate in Phase I of this study, you will be given this consent form.

There are two stages to the Phase I portion of this study: Stage 1 (dose escalation) and Stage 2 (expansion). Stage 1 (dose escalation stage) tested different doses of GDC-0032 in cohorts

(groups) of 3-6 subjects each. Approximately 7 dose levels of GDC-0032 were tested to study the safety of GDC 0032 during Stage 1.

In Stage 2, approximately 529-629 subjects will be enrolled in one of 19 cohorts (A, B, C, D, E, F, G, H, J, K, L, N, P, Q, R, S, T, and X). Subjects will receive GDC-0032 at the doses and schedules determined in Stage 1 and 2 to obtain further information on the safety and tolerability of the drug. Although this protocol includes many cohorts that enroll subjects with different types of cancer, you will only be enrolled into one of the cohorts that includes subjects with your type of breast cancer, which is called hormone receptor-positive breast cancer that is either locally advanced or metastatic. Hormone receptor-positive means that the cancer cells may receive signals from hormones like estrogen or progesterone that could promote their growth. Metastatic means that your cancer has spread to other parts of your body. This consent form only includes the information for cohorts that you may be enrolled into. The descriptions of these cohorts are below.

- In Stage 2 Cohort K, approximately 20 subjects with hormone receptor-positive breast cancer will be enrolled to assess GDC-0032 daily for 5 days followed by a 2-day break (5/2) when taken in combination with fulvestrant.
- In Stage 2 Cohort L, approximately 20 subjects with hormone receptor-positive breast cancer will be enrolled to assess GDC-0032 daily for 7 days followed by a 7-day break (7/7) when taken in combination with fulvestrant.
- In Stage 2 Cohort N, approximately 26 postmenopausal subjects with hormone receptor-positive breast cancer will be enrolled to assess GDC-0032 (2 mg) administered daily for 28 days when taken in combination with letrozole.
- In Stage 2 Cohort P, approximately 26 postmenopausal subjects with hormone receptor-positive breast cancer will be enrolled to assess GDC-0032 (4 mg) administered daily for 28 days when taken in combination with letrozole.
- In Stage 2 Cohort Q, approximately 20 postmenopausal subjects with hormone receptor-positive breast cancer will be enrolled to assess GDC-0032 administered daily for 21 days followed by a 7 day break (21/7) when taken in combination with letrozole.
- In Stage 2 Cohort R, approximately 20 postmenopausal subjects with hormone receptor-positive breast cancer will be enrolled to assess GDC-0032 administered daily for 5 days followed by a 2 day break (5/2) when taken in combination with letrozole.

- In Stage 2 Cohort S, approximately 20 postmenopausal subjects with hormone receptor positive breast cancer will be enrolled to assess GDC-0032 administered daily for 7 days followed by a 7 day break (7/7) when taken in combination with letrozole.

Some subjects enrolled in Cohorts K, L, N, P, Q, R, and S will be required to have a specific gene mutation, called a PIK3CA gene mutation, in their tumor cells to be allowed to participate.

If you are enrolled in Stage 2 of the study, then, depending on your type of cancer, you will be enrolled into one of these cohorts described above.

STUDY PROCEDURES

Pre-Treatment Period

Before you begin the study treatment period, you will be asked questions and will have tests done to make sure that you are able to participate in the study. Some of these tests may have been done already as part of your regular care. The information that will be collected and the tests that will be done at this time include the following:

- Discussion of this study and review and signing of the Informed Consent Form
- Recording of demographic information, including your age, sex, and race/ethnicity
- A review of your medical history and any medications and herbal or dietary supplements you are taking or have taken in the past 7 days

  Note: If you have received treatment at another hospital or facility, you will need to get a copy of your records.
- Measurement of your vital signs (blood pressure, breathing rate, temperature, and pulse), height, and weight
- A pulse oxygen test to measure the amount of oxygen in your blood. A small, painless, electrical sensor will be placed on one of your fingertips for this test.
- A complete physical examination will be done to assess any conditions that you have or have had
- Performance status evaluation (your ability to perform everyday tasks)
- Electrocardiograms (ECGs): An ECG measures the electrical activity of your heart and requires placement of electrical sensors on your chest, wrists, and ankles.
- Fasting (≥ 10 hour fast) laboratory blood tests for safety (including blood counts, blood chemistry tests to measure liver, pancreas, and kidney functions, blood clotting tests, white blood cell counts, cholesterol and fat levels, blood glucose and insulin, and

other safety tests). About 2-3 tablespoons of blood will be drawn for these safety laboratory tests.

- A urine sample for standard safety laboratory tests
- A blood or urine pregnancy test if you are a female of childbearing potential (even if you have had a tubal ligation)

  If you are pregnant, you will not be allowed to participate in this study.
- Imaging scans such as computed tomography (CT) or magnetic resonance imaging (MRI), etc., to assess your tumor

  A CT scan is a special test that produces an image of your body with the use of a small amount of radiation. The image shows the body tissues and structure in three dimensions (3-D).

  An MRI is a scan that uses radio waves and a strong magnetic field to provide images of internal organs and tissues.
- You will be asked to provide a sample of your tumor tissue from a previous biopsy or tumor excision to determine whether your tumor has specific gene mutations in the PI3K pathway and whether your tumor shows specific cancer proteins. These findings may provide clues as to how your tumor acts and how it may or may not be affected by GDC-0032. These tests may help explain why some people respond to treatment while others do not and why different people may respond differently to the study drug.
- Some subjects in Cohorts K, L, N, P, Q, R, and S must have a mutation in the PI3K gene in their tumor sample to take part in this study. You will be asked to undergo a new tumor biopsy if we cannot determine whether the PI3K gene in any prior tumor biopsy samples has a mutation.
- If you are enrolled in Cohorts N and P, at least 6 subjectswill provide fresh tumor tissue biopsy samples (before receiving GDC-0032 and during the GDC-0032 treatment period). Before you consent to participate in this study, your study doctor will tell you whether biopsy tumor tissue collection is required for your participation.

After your study doctor reviews the results of these screening tests, you may not be able to take part in this research study. If this happens, your study doctor will talk to you about the reasons for this decision, and will talk to you about other treatment options.

Study Treatment Period

You will begin the study treatment period once your questions have been answered, you have signed this consent form, and it has been determined that you meet the requirements for study participation.

During the study, you will need the following tests and procedures. They are part of regular medical care.

- Limited, symptom targeted physical examination
- Imaging scans (CT, MRI, etc.) typically done on cancer patients to assess the response of your cancer
- Measurement of your vital signs, including blood pressure, pulse, temperature, and weight
- A pulse oxygen test to measure the amount of oxygen in your blood

You will also have the following tests and procedures that are also part of regular medical care but are being performed more often for this study:

- Collection of up to about 1-2 tablespoons of blood for safety laboratory tests at each visit

You will need the following tests and procedures that are being used either to determine the effectiveness of GDC-0032 or to determine how GDC-0032 is being processed by or is affecting your body:

- Before receiving GDC-0032, blood samples for research on biomarkers, PI3K related mutations, pharmacogenetic analyses (analyses of links between your genetic makeup, and how your body processes GDC-0032). About 2 tablespoons of blood will be collected.

  Note: You will find information about the new Federal law called the Genetic Information Nondiscrimination Act (GINA) in the Privacy and Confidentiality section of this consent document.
- Collection of blood before dosing and at various times after dosing with GDC-0032. This will include samples for research on biomarkers and PI3K related mutations and how your body processes GDC-0032. If GDC-0032 is withheld for an adverse event, an additional sample may be collected. Up to about 5 ½ tablespoons of blood will be taken at each visit, depending on the specific visit day (see the Study Chart section).
- Collection of urine at different times to see how your body processes GDC-0032

- ECGs will be performed
- If you are enrolled in Cohorts L, N, Q, R, and S in Stage 2, you will also have an FDG PET imaging (which includes FDG PET or FDG PET/CT scan) performed within 14 days before beginning the study treatment period.

  For FDG PET imaging, a small amount of radioactive glucose (FDG) is given into your vein so a special scanning machine (a PET scanner) can measure how much glucose your tumors take in. The results of this test will be used to see whether glucose metabolism is affected by GDC-0032 and to help make sure the dose level tested in this study is appropriate for future studies. Sometimes a CT scan is also done at the same time of the PET scan with the use of a PET/CT scanner.

  A finger stick or blood sample will be taken to measure the glucose in your blood prior to the FDG PET imaging. You will be asked to fast before you come to the clinic by not eating anything, except for drinking water, for 4 hours before your test.

  If you are enrolled in Cohorts N or P, fresh biopsies of your tumor may be required (for at least 6 subjects in each cohort enrolled). Before you consent to participate in this study, your study doctor will tell you whether two fresh tumor biopsies will be taken, one before receiving GDC 0032 and one during the GDC-0032 treatment period in Cycle 1.

Blood samples (up to 1 ½ tablespoons) will be drawn for research on biomarkers and PIK3 related mutations at the clinic visits on Day 1 of every odd-numbered cycle following a confirmed partial or complete tumor response or progressive disease.

It may take many years to complete the research on the blood and tissue samples taken during the study, so your samples will be stored indefinitely or until they are all used up. Your blood, tissue, and/or fluid samples and related medical information will be used only for research and will not be sold. Your sample(s) will not be used for genetic testing to determine or predict risk of diseases that you do not currently have. Your samples will not be used for research involving human cloning (growing human tissue from this material).

Dose and Schedule of Study Drug

After completing the screening process, your doctor will determine whether you are eligible to participate in the study. If you are eligible and choose to participate, you will be assigned to receive a predetermined dose of GDC-0032, depending on when you enter the study. This is an open-label study, which means that you and your doctor will know the dose level and schedule of the study drug to which you are assigned and you will not get a placebo (an inactive substance). However, neither you nor your doctor may select which dose level or schedule of GDC-0032 you will receive or which stage you will be enrolled in.

The following will occur, depending on the stage and cohort (group) to which you are assigned:

In Stage 2 Cohort K, you will receive 4 mg GDC-0032 (tablet) daily for 5 days, followed by a 2-day break (5/2) for 28 days for each cycle, and fulvestrant on Days 1 and 15 of Cycle 1, and Day 1, only, of subsequent cycles. Fulvestrant is given intramuscularly in the buttocks as two injections, one in each buttock, (slowly, 1-2 minutes per injection), and will be given at the clinic.

In Stage 2 Cohort L, you will receive 4 mg GDC 0032 (tablet) daily for 7 days, followed by a 7-day break (7/7) for 28 days for each cycle, and fulvestrant on Days 1 and 15 of Cycle 1, and Day 1, only, of subsequent cycles. Fulvestrant is given intramuscularly in the buttocks as two injections, one in each buttock, (slowly, 1-2 minutes per injection), and will be given at the clinic.

In Stage 2 Cohort N, you will receive 2 mg GDC-0032 (tablet) and letrozole by mouth daily for 28 days (Days 1 to 28) of each cycle.

In Stage 2 Cohort P, you will receive 4 mg GDC-0032 (tablet) and letrozole by mouth daily for 28 days (Days 1 to 28) of each cycle.

In Stage 2 Cohort Q, you will receive 4 mg GDC-0032 (tablet) daily for 21 days, followed by a 7-day break (21/7) for 28 days for each cycle, and letrozole by mouth daily.

In Stage 2 Cohort R, you will receive 4 mg GDC-0032 (tablet) daily for 5 days, followed by a 2-day break (5/2) for 28 days for each cycle, and letrozole by mouth daily.

In Stage 2 Cohort S, you will receive 4 mg GDC-0032 (tablet) daily for 7 days, followed by a 7-day break (7/7) for 28 days for each cycle, and letrozole by mouth daily.

GDC-0032 is provided in a tablet. You will be given enough tablets to last until your next clinic visit. You will also receive a medication diary and will be asked to record the time and date of each dose of GDC-0032. At each visit, you will need to bring the diary to the clinic along with all unused medication for the study staff to review.

You should take all doses of GDC-0032 at approximately the same time each day (no earlier than 2 hours before and no later than 2 hours after the scheduled time). GDC-0032 Tablets will be swallowed whole (not chewed) with one glass (8 fluid ounces) of water.

If you miss a dose or vomit up a tablet of GDC-0032, you should skip that dose and start dosing with the next scheduled dose. You will not be allowed to make up missed doses.

Study Chart

The maximum length of study intervention in this study is 39 cycles, approximately 3 years. The chart on the next page shows what will happen to you during Cycle 1 and future study intervention cycles.

Tests and Procedures	Screening	Cycle 1		Cycle 2			**Cycles ≥ 3**		Study Completion/ Early Termination Visit
		Day 1	Day 15	Day 1	Day 15	Between Days 22 and 28	Day 1	Between Days 22 and 28	
Recording demographic information	X								
Review medical history	X								
Review medications and your health	X	X	X	X	X		X		X
Physical Exam	X	X	X	X	X		X		X
Weight	X	X	X	X	X		X		X
Vital Signs	X	X	X	X	X		X		X
Performance status	X			X			X		X
Pulse oxygen test	X	X		X					
ECG	X	X	X				X		X
Blood samples for safety laboratory tests (fasting ≥ 10 hr.)	X	X	X	X	X		X		X
Urine sample for safety laboratory tests	X								
Blood samples to measure how your body processes GDC-0032		X[f]	X[g]	X			X[c]		
Blood samples for research on biomarkers and PI3K-related mutation		X	X				X[d]		X
Blood samples to measure your blood sugar level		X							X
Pregnancy test	X								
CT scan/MRI	X					X[b]		X	
Bone Scan	X					X[a]			
FDG-PET Scan cohorts L and M only	X			X		X[e]			
Optional Biopsy	X		X						X
Take GDC-0032 in and record the dates and times in the study drug diary		Taken once a day according to drug diary (GDC-0032 will be given in the clinic Cycle 1 Day 1 and 15, Cycle 2 Day 1 and 15 and Cycle 3+ Day 1 only)							

Faslodex Administration in clinic (cohorts K,L)		X	X	X			X		
Letrozole Administration in clinic (cohorts N-S)		X		X			X		
Return unused GDC0-032 and review study drug diary				X			X		

Visits may occur within 1 day from the indicated days.

[a] If patient only has disease in bone, the bone scan should be at the end of Cycles 3, 6 and 8 and every 3 cycles (12 weeks) thereafter

[b] at the end of Cycles 2, 4, 6 and 8 and every 3 cycles (12 weeks) thereafter

[c] at Cycle 6 only

[d] prior to dosing at Cycle 3 Day 1 and Cycle 5 Day 1 and at clinic visits on Day 1 of every odd numbered cycle (e.g., Cycle 7 Day 1) subsequent to confirmed partial or complete tumor responses and/or at progressive disease (per RECIST) for any patient.

[e] to be done only if the doctor believes another scan would offer meaningful data

[f] cohort L and S only

[g] cohort K only

Study Completion/Early Termination Visit

If you complete the study (up to 3 years of study intervention) or withdraw from the study before you have completed all the scheduled visits or if your participation is ended by the study doctor or Genentech for any reason, you will be asked to return to the clinic for a study completion visit within 30 days (± 2 weeks) after your last dose of study drug(s) or before starting a new treatment regimen, whichever is earlier. The following assessments will be completed at this final visit:

- You will be asked to report any symptoms and health problems you have and any new medications you have started.
- You will have a limited physical examination, including measurement of your vital signs and weight.
- Your performance status will be determined.
- Have ECG measurements performed. You will be asked to return unused study drug and the patient diary for review.
- Fasting (≥ 10-hour fast) blood samples (about 1 tablespoon) will be drawn for routine laboratory tests.
- Blood (about 1 teaspoon) will be drawn to measure your blood sugar level.

- Blood samples (up to 2 ½ tablespoons) will be drawn to measure the level of GDC-0032 in your body
- You may have a biopsy to obtain a fresh tumor tissue sample.

You may have a tumor assessment by CT scan (and MRI or FDG PET, if needed) if you did not have one at the time of stopping study drug.

Safety Follow-Up

If you have an unresolved side effect during the study related to the study drug or procedures, it may be possible that the study doctor will ask you to visit the office for follow-up safety examinations or will call you by telephone for follow-up even after you have completed your regular study visits.

LONG-TERM FOLLOW-UP

If you discontinue from the treatment period of the study, you will be followed up for survival information and subsequent anti-cancer therapies. This information will be collected from you through telephone calls, your medical records, and/or clinic visits approximately every 3 months or until the study is terminated by Genentech. You will be followed for survival information unless you request to be withdrawn from study-survival follow-up. If you withdraw from the study treatment period but not from study follow-up, the study staff may use a public-information source (such as county records) to obtain information about your survival status, only.

How Long will I be in the Study?

You will be asked to take GDC-0032 for up to 3 years or until you experience unacceptable toxicity to the drug, your cancer gets worse, or the Sponsor ends the study.

The maximum length of time you will receive the study drug during this study is 3 years; however, if you are receiving benefit from study treatment, you may have the possibility of receiving the study drug beyond 3 years, at Genentech's discretion and provided study drug is available. If the study is terminated, however, study drug may not be offered after study termination.

When you complete the study (up to 3 years after the first dose of GDC-0032) or if you leave the study early, you will be asked to come back for a study completion or early termination visit. If you leave the study early, the study doctor will ask you to return to the clinic for a follow-up

examination approximately 30 days after your last dose of GDC-0032 or before you start another cancer treatment. Keeping in touch with you and checking on your condition will help the study doctor monitor any long-term effects of the study drug, GDC-0032.

If you have an unresolved side effect during the study, the study doctor may ask you to visit the office for follow-up examinations or will call you by telephone for follow-up, even after you have completed your regular study visits.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. The study doctor will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so that any potential risks from GDC-0032 can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he or she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped, even if you want to continue. Your participation in this study may be ended at any time for medical reasons or because Genentech finds it necessary to limit or stop this study. Genentech and the study doctor are not obligated to provide you with GDC-0032 after the study is over or has been stopped or after your participation in the study has ended.

If you decide to stop being in the study or if your study doctor stops you from taking part in the study, your study doctor will ask you to come back for a final study visit.

RISKS AND INCONVENIENCES

You may have side effects from the drugs or procedures used in this study, and they will vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, doctors and the study Sponsor do not know all the side effects that may happen, and there may be unknown side effects that could occur. Side effects can vary from mild to very serious. Your doctors may give you drugs to help lessen side effects. Many side

effects go away soon after you stop what is causing them. In some cases, side effects can be serious, long-lasting, and/or may never go away. There also is a rare risk of death. You should talk to your study doctor about any side effects that you have while taking part in the study.

GDC-0032 Side Effects

As of 30 July 2014, 115 subjects had receivedGDC-0032 alone at dose levels from 3 mg to 16 mg given daily. The following side effects (judged by the subject's doctors to be related to GDC-0032) were seen in 10% or more of subjects.

Common Side Effects

- Diarrhea (52%)
- Hyperglycemia (increased level of blood sugar) (35%)
- Nausea (35%)
- Fatigue (tiredness) (31%)
- Decreased appetite (25%)
- Rash (18%)
- Vomiting (13%)
- Stomatitis (inflammation of lining in mouth) (15%)
- Mucosal inflammation (12%)

Severe Side Effects (may result in hospitalization)

The following side effects of severe intensity were observed in subjects taking GDC-0032:

- Hyperglycemia (high blood sugar) (14%)
- Colitis (inflammation of colon) (6%)
- Rash (4%)
- Diarrhea (5%)
- A low level of potassium in the blood (5%)
- Pneumonitis (inflammation of lung tissue) (5%)
- Increased alanine aminotransferase increase (abnormal liver function test. which could indicate liver damage)
- Red blood cell count decrease (4%)
- Fatigue (4%)
- Abdominal pain (4%)

- A low level of sodium in the blood (3%)
- Increase in blood lipase (which could indicate pancreas damage) (3%)
- Shortness of breath (3%)A low level of phosphorous in the blood (3%)
- Pneumonia (3%)
- Urinary tract infection (3%)Congestive heart failure (2%)
- Infection with Clostridium difficile (2%)
- A low level of oxygen in the blood (2%)
- Decrease in blood neutrophils (a type of white blood cell) (2%)
- Pruritis (itchy skin) (2%)
- Respiratory failure (2%)
- Stomatitis (inflammation of lining in mouth) (2%)

As of 30 July 2014, a total of 115 subjects have received GDC-0032 and hormonal therapy (either letrozole or fulvestrant).

GDC-0032 Given Daily in Combination with letrozole in 28 Subjects

Common (Occurring in at least 10% of more of subjects) Side Effects judged by the subject's doctor to be related GDC-0032:

- Diarrhea (68%)
- Stomatitis (inflammation of lining in the mouth) (39%)
- Nausea (36%)
- Fatigue (29%)
- Decreased appetite (25%)
- Hyperglycemia (Increased levels of sugar in the blood (25%)
- Dysgeusia (distortion of taste) (21%)
- Mucosal inflammation (inflammation of moist surfaces like the lining of the mouth) (21%)
- Vomiting (21%)
- Dry skin (18%)
- Muscle spasms (18%)
- Asthenia (lack of strength) (14%)
- Dry mouth (14%)
- Pruritis (itchy skin) (14%)
- Increased aspartate aminotransferase (abnormal liver function test, which could indicate liver damage (11%)

Severe Side Effects (may result in hospitalization)

The following side effects of severe intensity were observed in subjects takingGDC-0032 in combination with letrozole:

- Diarrhea (14%)
- Asthenia (lack of strength) (7%)
- Increase in blood alkaline phosphatase (abnormal liver or bone function test, which could indicate liver or bone damage) (7%)
- Hyperglycemia (increased sugar levels in the blood) (7%)
- A low level of potassium in the blood (5%)
- Mucosal inflammation (inflammation of moist surfaces like the lining of the mouth)
- Stomatitis (inflammation of lining in the mouth) (7%)

GDC-0032 Given Daily in Combination with Fulvestrant in 87 Subjects:

Common (occurring in at least 10% of more of subjects) Side Effects assessed as related to GDC-0032:

- Diarrhea (64%)
- Nausea (32%)
- Fatigue (28%)
- Decreased appetite (25%)
- Mucosal inflammation (inflammation of moist surfaces like the lining of the mouth) (21%)
- Rash (21%)
- Asthenia (lack of strength) (18%)
- Hyperglycemia (increased levels of sugar in the blood) (17%)
- Colitis (inflammation of the colon) (16%)
- Stomatitis (16%)
- Dry skin (13%)
- Dyspepsia (indigestion) (12%)
- Dysgeusia (distortion of taste) (10%)

Severe Side Effects (may result in hospitalization)

The following side effects of severe intensity were observed in subjects taking GDC-0032 in combination with fulvestrant:

- Colitis (inflammation of colon) (12%)
- Diarrhea (10%)
- Hyperglycemia (increased blood sugar) (19%)
- Rash (5%)Increased aspartate aminotransferase (abnormal liver function test, which could indicate liver damage (3%)
- A low level of potassium in the blood (3%)
- A low level of sodium in the blood (3%)
- Decreased red blood cells (2%)
- Ascites (fluid accumulation in abdomen) (2%)
- Back pain (2%)
- Mucosal inflammation (inflammation of moist surfaces like the lining of the mouth) (2%)
- Pneumonia (2%)

Certain adverse events (e.g., rash, colitis, and pneumonitis) may also occur within 1-2 weeks of holding or stopping GDC-0032.

Perforated duodenal ulcers (i.e., hole that develops throughout the wall of the small intestine has been observed in 2 subjects who received GDC-0032 in combination with endocrine therapy. Appropriate caution should be taken with the administration of medications such as aspirin, nonsteroidal anti-inflammation drugs (e.g., ibuprofen, naproxen), and corticosteroids that can increase the risk of gastritis, peptic ulcers, or gastrointestinal perforation (i.e., hole that develops through the wall of the esophagus, stomach, or intestines).

Potential Drug Interactions:

GDC-0032 may interfere with proteins in the body called CYP enzymes that normally work to eliminate certain types of medications, over-the-counter herbal remedies, and some foods. Some medications may also interfere with the elimination of GDC-0032. Therefore, GDC-0032 may interact with certain foods or medications you may be taking. You cannot take quinidine or other cardiac anti-arrhythmic agents and any other anti-cancer treatments.

Because of the potential drug interaction of GDC-0032 with other medications, you need to tell the study doctor about all medications, herbal remedies, vitamins, and supplements you are

taking during the study so that your doctor can discuss your treatment options and your participation in the study with you. You should avoid St. John's wort, grapefruit juice, and grapefruit juice supplements. Drugs that should be avoided if possible include the following:

- Atazanavir, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, telithromycin, erythromycin, troleandomycin, fluconazole, itraconazole, ketoconazole, voriconazole, posaconazole, aprepitant, conivaptan, fluvoxamine, diltiazem, nefazodone, mibefradil, verapamil. rifampin, carbamazepine, phenytoin, oxcarbazepine, phenobarbital, efavirenz, nevirapine, etravirine, modafinil, and cyproterone

Allergic Reactions

There is a chance that you may experience an allergic reaction to GDC-0032. Allergic reactions may be mild (such as skin rash or hives) to severe (such as breathing difficulties or shock). A severe allergic reaction would require immediate medical treatment and could result in permanent disability or death.

Sun Exposure

There is a chance that GDC-0032 may make your skin more sensitive to the sun. Therefore, it is recommended that you avoid prolonged sun exposure and that you apply protective sunscreen and lip balm as appropriate while on study.

As with any drug, unanticipated side effects, some of which may be potentially life-threatening, may occur that have not been previously reported. Please tell your doctor about any symptoms you have while you are taking part in this study.

LETROZOLE SIDE EFFECTS

The following side effects have been observed in subjects treated with letrozole:

- Bone effects (may include bone pain, decreases in bone mineral density, and bone fractures)
- Increases in blood lipid levels, fatigue, dizziness, hot flushes, back pain, nausea, joint pain and sweating
- Shortness of breath and possible risk of heart problems or problems with blood clots

FULVESTRANT SIDE EFFECTS

The following side effects were observed in patients treated with fulvestrant:

- Injection site pain, muscle, joint and bone pain, nausea, hot flashes, headache, tiredness, vomiting, loss of appetite, weakness, cough, constipation, shortness of breath and increased liver enzymes

Other Risks of the Study

Blood Draws:

There is also a small risk of side effects from drawing blood for the tests that you will have throughout the study. The side effects that may occur when you have blood drawn are listed below.

Care will be taken to avoid these side effects:

- Fainting
- Redness
- Pain
- Bruising
- Bleeding
- Infection

If you feel faint, tell the study staff right away.

ECGs:

Electrodes will be attached to your skin on select locations of your body (arms, legs and chest). The areas where the electrodes will be placed will be cleaned; some areas may need to be shaved. Once the electrodes are placed, the test will begin. The test is painless and usually takes less than a minute to perform. After the test, the electrodes are removed. You may experience some discomfort with placement or removal of the adhesive patches.

Radiation and Contrast Material:

CT and MRI scans are special tests used to study the internal organs of your body and are necessary to measure your response to this treatment. You will be exposed to radiation from the CT scans approximately every 8 weeks. Your exposure to radiation is limited and poses minimal risk to your health. In addition, you would likely undergo these scans even if you did not participate in this study because your doctor would need to monitor your cancer. Therefore, your participation in this study would not likely increase your radiation exposure from these CT scans.

As part of the CT scans, contrast material may need to be taken by mouth and/or injected into your vein to make certain organs and tumor sites visible on the scan. Oral (by mouth) contrast may cause side effects such as nausea, constipation, diarrhea, and abdominal bloating. Pain, bruising, redness, swelling, and/or infection may occur at the site where a needle is inserted to administer the contrast material into your vein. You may have an allergic reaction to the contrast material that could cause rash, hives, shortness of breath, wheezing, and itching and rarely may cause your heart to stop beating ("cardiac arrest"). The use of contrast material during these tests would be a normal part of measuring response of your cancer to therapy even if you were treated outside of a clinical trial. Lastly, you may feel uncomfortable during the tests, since you are not allowed to move during the picture, and you may experience claustrophobia (fear of being in small places).

For more information about side effects and risks of CT scans, contrast materials, or MRI scans, ask your study doctor.

FDG-PET Scans:

For FDG-PET imaging (which includes FDG-PET or FDG-PET/CT scans), a small amount of radioactive glucose (FDG) is given into your vein so a special scanning machine (a PET scanner) can measure how much glucose your tumors take in. The scan will be reviewed by a doctor and if it is determined that glucose can be measured in the tumor, then you will be asked to have repeat scans during the study. The results of this test will be used to see whether glucose metabolism is affected by GDC-0032 and to help make sure the dose level tested in this study is appropriate for future studies.

Each FDG-PET scan requires fasting (water and other medications only) for at least 4 hours prior to the test. You will be asked to avoid tiring activity about 24 hours before the test and have a low-carbohydrate diet the day before the scan. You will have a pinprick or blood draw to determine your glucose levels prior to each scan, and they must be within a reasonably normal range or the scan may need to be rescheduled. You will receive an intravenous (IV) injection with a small amount of radioactive tracer. You will be asked to remain motionless and the scan should itself take approximately 30 minutes. You will also have one blood sample drawn on the day of the second FDG-PET scan to determine the blood levels of GDC-0032.

There may be some discomfort similar to a pinprick for the IV delivery of the radioactive tracer used in these scans. There may be pain and a small risk of bruising and/or infection at the place where the needle is inserted. Also, there might be some anxiety and claustrophobia (an

abnormal fear of being in narrow or enclosed spaces) associated with the scanner. These scans require a small amount of radioactive material but are considered safe and these scans are routinely done in patients with cancer.

If you have FDG-PET/CT scans, then a CT scan is also done at the same time. The risks of CT scans are described above under the section named "Radiation and Contrast Material."

For more information about side effects and risks of FDG-PET imaging, ask your study doctor.

Tumor Biopsy:

In most subjects, collection of biopsy samples of tumor tissue will be performed with a special needle, called a core biopsy needle. The core biopsy needle allows the doctor to remove a small piece of that tissue that can later be evaluated under a microscope. The safety of collecting biopsy samples of tumors in internal organs is enhanced by doing this procedure under CT guidance. The CT scan will help the doctor locate the tumor tissue, avoid vital structures like blood vessels, and place the needle into the tumor tissue. Unless the tumor tissue is a lump in the skin or in a lymph node just under the skin (superficial), the collection of tumor biopsy samples for this optional research will be done under CT scan guidance. The risks of the tumor biopsy procedure are mainly pain, bleeding, and infection. Depending on the location of the tumor, there is a small risk of injury or damage to the nearby organs or tissues. Your doctor may use a local anesthetic or a medicine to calm your nerves before or during the biopsy procedure. Your doctor will explain the procedure to you and discuss these comfort measures.

Risks to Reproduction, Unborn Babies and Nursing Infants

In rat studies, undesirable side effects on ovaries and unborn fetuses were observed. It is not known what these effects seen in rats will have in women who are trying to get pregnant, women who are pregnant, and/or on an unborn/newly born baby.

Female subjects must not become pregnant and male subjects must not impregnate a female partner while in this study. The effects of these drugs on an unborn baby are not known, and could be harmful. You may not take part in this research study if you are pregnant or are a nursing mother. Women should not breastfeed a baby while on this study.

If you are able to become pregnant or able to get a woman pregnant, you must use two forms of birth control that are approved by your study doctor while you are in the study.

If you know or think that you or your partner may be pregnant during this time, you must notify your doctor immediately. You will be removed from the study if you become pregnant during the time you are receiving the study drug.

Women

If you are able to become pregnant, you must have a negative pregnancy test before you start the study treatment period.

If you are a woman capable of having children, you must use at least two of the following types of birth control while you are in this study and for 3 months after your last dose of the study drug. One of these methods must be double barrier method; for example a condom or diaphragm plus spermicidal agent (foam/gel/cream/film/suppository). Additional methods are:

- Abstinence (no sex)
- IUD or IUS (intrauterine devices or intrauterine system with the exception of IUD progesterone T)
- Vasectomy of any and all male partners
- Use of approved oral, injected, or implanted hormonal methods of contraception. This must be approved by your study doctor before you begin taking the study drug.

Even if you use birth control during the study, there is still a chance you could become pregnant.

Men

If you are a man, acceptable methods of birth control include using one of the following while you are in this study and for 3 months after your last dose of the study drug (due to the unknown effects of the study drug on the sperm):

- Abstinence (no sex)
- Condom plus spermicidal agent (foam gel/cream/film/suppository) plus **a secondary method**. Acceptable secondary methods include: vasectomy or partner's use of an IUD/IUS (intrauterine devices or intrauterine system with the exception of IUD progesterone T).

You must not donate sperm during this study and for 3 months after the last dose of the study drug.

BENEFITS:

If you agree to take part in this study, there may or may not be direct benefits to you. There is no guarantee that you will receive personal benefit from participating in this study.

Information from this study may help other cancer patients in the future.
Your samples will be owned by Genentech. If a commercial product is developed from this research study, rights to the commercial product will belong to Genentech and its collaborators (persons or companies partnering with Genentech). You and your family will not receive any financial benefits or compensation from or have rights in any developments, inventions, or other discoveries that might come out of this research.

ECONOMIC CONSIDERATIONS:

You will not be paid for your participation in this study. The study drug, GDC-0032, will be provided free of charge by Genentech, Inc., while you are participating in this study. Fulvestrant and letrozole, will be provided free of charge by Yale Cancer Center.

You will be responsible for certain procedures related to your care while on this clinical trial. This is also referred to as standard of care (SOC). The following procedures performed during your participation in this trial are considered SOC and you or a third party will be responsible for the associated charges:

- Medical history
- Laboratory tests (chemistry and hematology samples)
- Physical exams
- Imaging Scans (CT Scans, FDG-PET Scans and MRI)

In addition, there are some study procedures that are directly due to your taking part in this study and will be provided at no cost to you. Neither you nor your insurance company will be charged for the following items that are being done for research purposes:

- Study drugs (GDC-0032, Fulvestrant and Letrozole)
- ECGs

- Study visits
- Tumor biopsies
- Study laboratory tests (pregnancy test, urine samples and blood samples for research on biomarkers, PI3K related mutations, pharmacogenetics and to measure how your body processes GDC-0032)

Therefore, you should not claim these costs from your insurer.

The study Sponsor does not intend to continue providing GDC-0032 or any other study-related procedures to you after the end of the study or if you choose to withdraw from the study. After your participation in the study ends, you or your health plan will need to pay for medicines and clinic, hospital, and doctors' services that are part of your regular medical care. The Roche (Genentech) Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

TREATMENT ALTERNATIVES:

There are other treatments available to you if you decide not to take part in this study. Other investigational treatments, standard anti-cancer therapies, or anti-cancer drugs may be available for you. You may choose to treat your symptoms only, and not to have any anti-cancer therapy. Please talk to your doctor about all of your options.

During the study, we will tell you about new information or changes in the study that may affect your health or your willingness to continue on the study. When informed of this new information, if you agree to continue on the study, you will be asked to sign an updated consent form.

CONFIDENTIALITY AND PRIVACY:

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information.

If you sign this document, you give permission to use or disclose (share) your health information that identifies you only for the purposes of this research study and for research directly related to cancer and related diseases and/or the use of GDC-0032 in disease therapy and diagnosis. This may include information that might directly identify you, such as your name, date of birth and medical record number**.** This information will be de-identified prior to providing it to the sponsor, meaning we will replace your identifying information with a code that does not directly identify you.

Your medical information will be kept as confidential as possible within the limits of the law. Your medical information may be given out if required by law. If information from this study is published in a medical journal or presented at scientific meetings, you will not be identified by name, picture, or any other personally identifying information.

The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. The records for this trial will be stored in locked cabinets and/or offices and password protected computers. The research team will only give this coded information to others to carry out this research study or to sponsor representatives to comply with federal laws and regulations such as those related to Medicare reporting.

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g., health insurance company, disability provider.)

The information about your health that will be collected in this study includes:

- Research study records
- Medical and laboratory records of services provided during your participation with this study and your past medical history

Information about you and your health which might identify you may be used by or given to:

- Representatives from Yale University and the Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are

responsible for ensuring research compliance. These individuals are required to keep all information confidential.

- Your providers who are participants in the Electronic Medical Record (EMR) system
- Those individuals at Yale and the SCRI Clinical Trial Management Office (CTMO) who are responsible for the financial oversight of research including billings and payments
- The study doctor, Dr. Lajos Pusztai, and the Yale research team
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the new drug product involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- The study sponsor (Genentech, Inc.), their representatives, study monitors, collaborators, and licensees (people and companies partnering with the sponsor)
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study
- Data managers at the Yale Cancer Center, who enter information into the study database for research purposes.
- Qualified researchers

  Your medical and personal information may be shared with qualified researchers who are not participating in this study, for research purposes and to advance medical care and science. In such cases, additional steps will be taken to protect your information from being linked to you. Before receiving your medical and personal information, the researchers have to agree that they will use it for research purposes only and that they will not make any attempts to trace your information back to you.

Your genetic research data may be shared with researchers who are not participating in this study or submitted to government or other health research databases for broad sharing with other researchers. You will not be identified by name or any other personally identifying information.

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing

is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However to better protect your health information; agreements are in place with these individuals and/or companies that require that they keep your information confidential. Review of your medical records by these people or groups of people will not violate your confidentiality.

The sponsor will see the research information we collect about you when they come to Yale to monitor the conduct of this research study. The "Sponsor" includes any persons that work for or are hired by the sponsor to conduct research activities related to this study. For this study the sponsor includes Genentech, Inc. Yale researchers will also send the sponsor your health information during the study or at the end of the study. When Yale researchers send information about you to the sponsor, they will not send information that directly identifies you such as your name or birth date.

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

You do not have to sign this consent form, but if you do not, you may not take part in this research study. You are free at any time to limit the use and sharing of your health information, without penalty or other consequence. However, you may not be allowed to take part or continue to take part in this research study if at any time you choose to limit the use and sharing of your health information that is necessary for the completion of this research study.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, by signing this consent form, you agree that you will not be able to review or receive some of your records directly related to the study until after the entire study has been completed.

Your authorization (permission) to use and disclose (share) your health information will continue indefinitely, but that use and sharing will be only for the purposes described in this Informed Consent Form.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

IN CASE OF INJURY:

If you have any side effects after taking the study drug or are injured during the study, tell your Study Doctor right away. Your Study Doctor will make sure you receive medical treatment.

Genentech will pay for the reasonable costs of diagnosis and treatment of any adverse reaction, illness, or physical injury that specifically results from the study drug or from non-standard of care drugs or procedures, but only if:

- Genentech and the study doctor agree that your injury resulted from the study drug (GDC-0032) and not from a preexisting medical condition;
- Your injury did not result from a failure to follow study protocol or instructions, or from the negligence, mistakes, or misconduct of the study personnel.

You will not receive any other kind of payment. There are no plans to pay you for such things as lost wages, disability, or discomfort as part of this study. You do not give up any of your legal rights by signing this consent form.

VOLUNTARY PARTICIPATION AND WITHDRAWAL:

Withdrawing From the Study:

You are free to choose not to take part in this study; your participation in this study is voluntary. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. They will make sure that proper procedures are followed and a final visit is made for your safety. This will cancel any future research study appointments.

The researchers, your doctor and/or the Sponsor (Genentech, Inc.) may withdraw you from participating in the research if necessary and without your consent at any time, for any of the following reasons:

- If it is in your best interests;
- If your disease worsens;
- If you experience serious side effects;
- If you do not follow the study instructions;
- Pregnancy;
- If you do not later consent to any future changes that may be made to the study plan;
- For any other reason.

If this happens, your doctor will discuss further treatment options with you.

If you choose not to participate or if you withdraw it will not harm your relationship with your own doctors or with Yale-New Haven hospital.

If you fail to give your consent by not signing this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any treatment provided as part of the study. Unless and until you do cancel the consent, it will remain valid and effective.

Withdrawing Your Authorization to Use and Disclose Your Health Information:

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by telling the study staff or by sending written notice to the study doctor Lajos Pusztai, MD at the address listed on page one of this form. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

QUESTIONS: We have used some technical terms in this form. Please feel free to ask about anything you do not understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project as described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use and give out information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to participate in this research.

Study Participant (print name)	Signature	Date
Person obtaining consent (print name)	Signature	Date
Person obtaining consent (print name) – only if applicable, otherwise blank	Signature	Date
Interpreter/ Witness (print name) – only if applicable, otherwise blank	Signature	Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Lajos Pusztai at 203-737-8309. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.