AN OPEN-LABEL, PHASE Ia/Ib/IIa STUDY OF GDC 0810 SINGLE AGENT OR IN COMBINATION WITH PALBOCICLIB AND/OR AN LHRH AGONIST IN WOMEN WITH LOCALLY ADVANCED OR METASTATIC ESTROGEN RECEPTOR POSITIVE BREAST CANCER

Published: 02-03-2015
Last updated: 16-04-2024

Primary ObjectivePhase Ia* To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D)and assess the safety of single agent GDC-0810 in postmenopausal women with locally advanced or metastatic estrogen-receptor-positive (ER...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON45124

Source
ToetsingOnline

Brief title
Genentech GO29642

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Estrogen receptor positive breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Genentech, Inc
Source(s) of monetary or material Support: Pharmaceutical company

Intervention

Keyword: GDC-0810, locally advanced or metastatic ER+ (HER2-) breast cancer

Outcome measures

Primary outcome

1. Maximum tolerated dose (MTD)

2. Incidence of adverse events

3. Efficacy (phase II portion only):clinical benefit rate according to

RECIST v1.1

Secondary outcome

1. Maximum tolerated dose (MTD)

2. Incidence of adverse events

3. Efficacy (phase II portion only):clinical benefit rate according to

RECIST v1.1

Study description

Background summary

Breast cancer is the most common form of cancer in women, accounting for more than 1,300,000 new cases and nearly 500,000 cancer deaths annually (Jemal, 2011). Approximately 80% of all breast cancers express and are dependent on the estrogen receptor (ER) for tumor growth and progression. Modulation of estrogen activity and/or synthesis is the mainstay of therapeutic approach in postmenopausal women with ER-positive (ER+) breast cancer. However, despite

the effectiveness of available hormonal therapies such as tamoxifen, aromatase inhibitors and full ER antagonists/degraders, many patients ultimately relapse or develop resistance to these agents and therefore require further treatment for optimal disease control. As such, there is a need for the development of new ER-targeting therapies with increased anti-tumor activity to further delay disease progression and/or overcome resistance to the currently available hormonal therapies and ultimately prolong survival in postmenopausal women with ER+ advanced breast cancer.
Despite becoming refractory to aromatase inhibitors or tamoxifen, growth and survival of resistant tumor cells remain dependent on ER signaling; therefore, patients with ER+ breast cancer can still respond to second/third line hormonal treatment after progression on prior hormonal therapy (Di Leo, 2010; Baselga, 2011). An agent with a dual mechanism of action (ER antagonism plus degradation) has the potential to target both ligand-dependent and independent ER signaling and, consequently, improve treatment outcomes in late stage ER+ breast cancer. Furthermore, recent studies have identified mutations in ESR1 affecting the ligand-binding domain (LBD) of the estrogen receptor. Mutant receptors drive ER-dependent transcription and proliferation in the absence of estrogen and reduce the efficacy of ER antagonists, suggesting that LBD-mutant forms of ER are involved in mediating clinical resistance to endocrine therapy and that more potent ER antagonists may be of substantial therapeutic benefit (Toy, 2013; Robinson, 2013; Li, 2013).
GDC-0810 is a novel, potent ER-* antagonist and inducer of ER-* degradation that is being developed for the treatment of postmenopausal women with ER+ advanced breast cancer whose disease has recurred or progressed following treatment with hormonal therapy. In murine MCF-7 xenograft models, GDC-0810 has demonstrated robust tumor regression in both tamoxifen-sensitive and tamoxifen-resistant models. Based on its bipartite activity profile, the nonclinical efficacy in tamoxifen-sensitive and tamoxifen-resistant xenograft studies, and nonclinical safety profile, GDC-0810 has the potential to be an important therapeutic drug for the treatment of postmenopausal women with ER+ advanced breast cancer.

Study objective

Primary Objective
Phase Ia
* To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D)and assess the safety of single agent GDC-0810 in postmenopausal women with locally advanced or metastatic estrogen-receptor-positive (ER+) and human epidermal-growth-factor-negative (HER2-) breast cancer

Phase IIa
* To determine the anti-tumor activity of single agent GDC-0810 in

Secondary Objectives:
Phase Ia

* To evaluate the pharmacokinetics of GDC-0810 single agent and its glucuronide metabolites following single and multiple dose treatments.
Phase IIa
* To evaluate the safety of GDC-0810 single agent when administered at the RP2Ds in women with locally advanced or metastatic ER+ (HER2-) breast cancer
* To evaluate the effect of GDC-0810 single agent on ventricular repolarization in postmenopausal women participating in the Phase IIa portion of the study

Exploratory Objectives:
* To perform exploratory evaluation of biomarkers of pharmacodynamic (PD) response with [18F]-fluoroestradiol (FES) positron emitting tomography (PET) in Phase Ia and Phase IIa
* To perform exploratory evaluation of ER target genes expression
* To perform exploratory evaluation of mechanisms of resistance to GDC-0810

Study design

This is a multi-institution Phase Ia/Ib/IIa open-label, dose-finding, safety, PK, and proof of concept study of GDC-0810 as a single agent and in combination with palbociclib and/or LHRH agonist.
The study is divided into three phases: Phase Ia, Phase Ib, and Phase IIa. The Phase Ib palbociclib combination cohorts will be conducted in the U.S. only and the LHRH agonists combination cohorts will be conducted in the U.S. and South Korea. The Phase Ia and IIa part of the study (single agent GDC-0810 cohorts) will be conducted in Spain, Netherlands South Korea and the U.S.
Enrollment in Study GO29642 has been discontinued; therefore, no patients will be enrolled in the Phase Ib Cohorts C2, C3, and D2. Any patient currently enrolled in Phase Ia, Ib Cohort C1, Ib Cohort D1, or IIa experiencing clinical benefit may continue to receive GDC-0810 as a single agent or combination with LHRH agonist or palbociclib until disease progression, unmanageable toxicity, patient withdrawal of consent, GDC-0810 drug supply has been exhausted, or the Sponsor terminates the study.

Phase Ia
Phase Ia consists of dose escalation in postmenopausal women with locally advanced or metastatic ER+ (HER2-) breast cancer and enrollment into dose escalation cohorts has been completed.
Phase Ia consists of dose escalation in postmenopausal women with locally advanced or metastatic ER+ (HER2-) breast cancer.
During Phase Ia, GDC-0810 single agent was administered orally to postmenopausal women with locally advanced or metastatic ER+ (HER2-) breast cancer on a continuous daily dosing regimen with a Day -7 lead-in period for single dose PK evaluation prior to the start of daily treatment. The incidence of dose-limiting toxicities (DLTs) will be evaluated from Day -7 through the first cycle (28 days) of treatment (35 days total). Depending on safety and tolerability, patients will be assigned sequentially to escalating doses of GDC 0810 using standard 3 + 3 design.

The starting dose will be 100 mg once daily. Dosing will be based on flat milligram increments without adjustments for body size. It is anticipated that dose levels will span the anticipated pharmacologically active dose range and be within the safety margin indicated by nonclinical toxicology studies. The dosing regimen may be changed if the PK and safety data suggest that a discontinuous regimen or another dosing frequency (e.g., twice daily [BID]), with or without a fasting requirement, may be preferable for the Phase IIa portion of the study.

Phase IIa
Expansion cohorts consisting of a total of 100 postmenopausal women with locally advanced or metastatic ER- (HER2-) breast cancer previously treated with an aromatase inhibitor (AI) will be treated at the RP2D to further characterize the safety, PK, PD, and anti-tumor activity of GDC-0810 as follows:
Cohort A: 30 patients who have confirmed ER+ (ESR1) mutation of the ligand binding domain (LBD), further divided into 2 subsets:
Cohort A1: 20 patients who had no prior treatment with fulvestrant. FES-PET will be obtained for PD analysis only in Cohort A1.
Cohort A2: 10 patients where prior treatment with fulvestrant is allowed
Cohort B: 70 patients who have progressed following 1 prior therapy with an AI in the advanced/metastatic setting, further divided into 2 subsets:
Cohort B1: 50 patients who had no prior treatment with fulvestrant
Cohort B2: 20 patients where prior treatment with fulvestrant is allowed

During the Phase Ib and Phase IIa portion of the study, there will be no PK week lead in period (i.e., all eligible patients will start continuous daily dosing treatment on Cycle 1 Day 1).
The effect of GDC-0810 on ventricular repolarization will be evaluated in all patients enrolled in the Phase IIa portion of the study.
After enrollment is complete in Cohorts A2, B1, and B2 of the Phase IIa portion of the study, further enrollment in Cohort A1 may be discontinued. Enrollment in the Phase IIa portion of the study is complete.
All patients will be treated until disease progression, unacceptable toxicity, or patient withdrawal of consent.

Intervention

At the MTD and/or RP2D, a total of 100 patients will be enrolled to further assess the safety, tolerability, and preliminary evidence of anti-tumor activity and exploratory pharmacodynamic markers of response of GDC-0810 in 3 distinct patient populations (Cohorts A1 and A2 will be combined for analysis purposes). Future clinical development of GDC-0810 as a single agent will likely depend on the results observed from these 3 cohorts of patient

Study burden and risks

The most common side effects (i.e., occurs in more than 10 out of 100 patients with breast cancer) considered by the study doctor to be related to GDC-0810 were as follows: Diarrhea, Nausea, Fatigue (feeling tired), Hot flashes and flushing, Constipation, Vomiting, Heartburn, Decreased appetite, Flatulence, Anemia (low levels of red blood cells that can make you feel tired or breathless), Abdominal discomfort or pain, Dry mouth, Muscle pains and aches, High levels of liver enzymes (chemicals made by the liver, which can indicate damage to the liver if elevated), Disturbance of taste, Vaginal discharge, Low counts of white blood cells.

Less common side effects (i.e., occurs in 1 * 10 out of 100 patients) considered by the study doctor to be related to GDC-0810 were as follows: Abdominal swelling, Swelling of areas such as the arms and legs with fluid (edema), Sore throat or mouth, Difficulty breathing, Dizziness, Dry skin, Headache, Low blood pressure, Insomnia (difficulty sleeping), Night sweats, Deep vein thrombosis (blood clots, usually in the legs that can on occasion cause serious or life threatening health problems), Dryness in the vaginal area, Pain in the joints, Back pain, Low levels of phosphate (a chemical in the blood important for proper functioning of your cells), Chalazion (a red, painful swelling on the eyelid), Cataract (a problem with the lens of the eye making it turn cloudy), Rash and itching, High triglycerides (fats in your blood), High levels of cholesterol in the blood, Soreness and irritation of the mouth, gums, and lips or other mucous membranes, Pulmonary embolism (blood clots in the lungs that can cause serious or life threatening health problems), Swelling of the face, Ringing in the ears, Enlargement of the lining of the womb (endometrium), Polyps in the uterus (growths in the womb that may be benign or may be early signs of cancer), Bleeding from the vagina, High blood sugar, High levels of a chemical called uric acid in the blood. If severe, this can cause gout (a painful joint problem) or cause damage to the kidneys, Low levels of magnesium, sodium, chloride and potassium in the blood (important minerals that if severely low can lead to problems with the heart, kidneys or health in general), High levels of magnesium in the blood, Weight loss, Damage to the nerves in the arms, legs, hands, and feet, which may result in numbness, tingling, or pain, Anxiety and depression, Irritability, Palpitations of the heart, Bleeding hemorrhoids, Low levels of albumin in the blood (a protein important for many aspects of general health), Pain in the face, chest, arms/legs or breast, Discomfort or pain when having sex, Increase in lactate (a chemical that can indicate damage to tissues if increased), Disturbance of hormones that control the thyroid, Low platelet counts (small cells that are important for the clotting of blood), Cough, Runny nose, Need to suddenly pass water, Acne, Hair loss, Increase levels of alkaline phosphatase, a protein in the blood that can indicate damage to liver or bone, Soft stool.

As of August 2015, blood clots have been seen in five subjects with breast cancer who received GDC-0810, including one who suffered a life-threatening clot in the lungs. This subject was treated with drugs to thin the blood and was able to continue in the study. Blood clots can potentially be serious or

life-threatening. If you experience discomfort or swelling in the arms or legs, shortness of breath, difficulty breathing, or pain in the chest, please inform your study team immediately.
Diarrhea is the most common side effect of GDC-0810 and is generally manageable and tolerable. In rare cases it can be severe, but your study doctor will monitor you closely for this.

Other Risks:
Because GDC-0810 blocks the action of female sex hormones, it may also contribute to loss of muscle and bone and likely lead to hot flashes, vaginal dryness or discharge, irritation, mood swings, and decreased interest in sex. Adverse events in animal studies where animals were treated with high doses of GDC-0810 included diarrhea, vomiting, reduced appetite, dehydration, reduced body weight, and reduced body temperature. It was also observed that in rats, some of the animals had ovarian cysts (a closed sac that develops abnormally on one or both ovaries), changes in the appearance of the vagina (paleness or thinning), and changes in the appearance of the uterus. The weights of certain body parts (adrenal gland, pituitary gland, uterus, and ovarian) either decreased or increased.

There are also risks or discomforts associated with blood draws, biopsies, and radiation exposure from the imaging studies.

Risk of blood drawing: As with all blood drawing for the purpose of obtaining samples, there is a risk of bruising, pain, or infection at the site of the blood draw.

Radiation risks from imaging studies: As part of this study you will have CT/ MRI, and bone scans which involve exposure to radiation. The amount of radiation exposure you may receive from these standard diagnostic tests is considered small, and will not adversely affect the treatment of your disease. In addition, you may also have FES-PET scans, which are considered for research purposes only. The scan involves injecting a small amount of radioactive material into your vein. The radioactive material travels through your blood to reach the tumors. As it wears off, it gives off a small amount of radiation. All radiation will be gone from the body within a day. The risk is probably no greater than with routine or conventional x-rays. Other potential risks are rare, but may include an allergic response.

Contrast dye for imaging scans: Contrast dye is usually administered when you get a CT or bone scan. Some people may develop hives and itching or other allergic symptoms from this dye. In addition, if you have low kidney function, this dye can temporarily or permanently decrease your kidney function.

MRI (Magnetic Resonance imaging) scans: As part of this study you may have an MRI scan. A MRI scan involves a strong magnetic field so please tell your

doctor if you have a pacemaker (the magnetic field can cause your pacemaker to malfunction), metal dental work or a metal prosthesis (implant) in your body. Also MRI scans require you to be in a small space, so please tell your study doctor if you have claustrophobia (fear of being in a confined space).

Biopsies: The risks and complications associated with collecting tumor samples include those related to anesthesia and those related to any type of surgery. Risks related to anesthesia include, but are not limited to stroke, kidney failure, pneumonia, and blood clots. Risks related to surgery include infection and bleeding either during or after the biopsy, which may necessitate a blood transfusion or another surgery. Fluid may collect under the skin, which may need to be taken out with a needle. Finally, skin scars may result from the biopsy which may be painful or cosmetically unattractive.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Phase IIa Inclusion Criteria:
- Signed and dated informed consent document indicating that the subject (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment
- Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either locally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease, both progressing after at least 6 months of hormonal therapy for ER+ breast cancer
- ER-positive, HER2-negative
- At least 2 months must have elapsed from the use of tamoxifen
- At least 2 weeks must have elapsed from the use of any other anticancer hormonal therapy
- At least 3 weeks must have elapsed from the use of any chemotherapy
- Females, 18 years of age or older
- Postmenopausal status
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Adequate organ function
- Cohort A only: Confirmed ESR1 mutation of the LBD and presence of measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or evaluable bone disease
- Cohort A1 only: no prior fulvestrant allowed; at least 2 months must have elapsed from the use of tamoxifen
- Cohort A2 only: prior fulvestrant allowed
- Cohort B only: disease progression following prior treatment with an aromatase inhibitor in the advanced/metastatic setting
- Cohort B1 only: no prior fulvestrant allowed
- Cohort B2 only: prior fulvestrant allowed

Exclusion criteria

Phase IIa Exclusion Criteria
- Untreated or symptomatic CNS metastases
- Patients with a history of endometrial polyps, endometrial cancer, atypical endometrial hyperplasia, or other significant endometrial disorders should be excluded unless they have undergone total hysterectomy and there is no evidence of active disease.
- More than 2 prior chemotherapy in the advanced/metastatic setting (prior adjuvant chemotherapy is allowed so long as it occurred >/= 12 months prior to enrollment)
- Current treatment with any systemic anticancer therapies for

advanced disease or any systemic experimental treatment on another clinical trial
- Any significant cardiac dysfunction within 12 months prior to enrollment
- Active inflammatory bowel disease e.g. Crohn*s disease or ulcerative colitis), any active bowel inflammation (including diverticulitis), or chronic diarrhea, short bowel syndrome, or upper gastrointestinal surgery including gastric resection
- Known human immunodeficiency virus infection
- Major surgery within 4 weeks prior to enrollment
- Radiation therapy within 2 weeks prior to enrollment
- Cohort A1, A2, and Cohort B2 only: > 1 prior chemotherapy in the advanced/metastatic setting
- Cohort B1 only: prior chemotherapy in the advanced/metastatic setting

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-12-2015
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GDC-0810
Generic name:	-

Ethics review

Approved WMO Date:	02-03-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-08-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-04-2016

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-004852-77-NL
ClinicalTrials.gov	NCT01823835
CCMO	NL52492.042.15