ForPatients
by Roche

OncologyLocally Advanced or Metastatic Breast CancerBreast CancerEstrogen Receptor (ER)-PositiveHER2-Positive Breast Cancer

A clinical trial to compare how effective and safe giredestrant plus pertuzumab and trastuzumab is compared to pertuzumab and trastuzumab with or without hormone therapy in people with locally advanced or metastatic breast cancer, with HER2 and oestrogen receptor positivity

A Study to Evaluate the Efficacy and Safety of Giredestrant in Combination With Phesgo (Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf) Versus Phesgo in Participants With Locally Advanced or Metastatic Breast Cancer (heredERA Breast Cancer)

Trial Status	Trial Runs In	Trial Identifier
Recruiting	30 Countries	NCT05296798 2022-500014-26-00 WO43571

The information is taken directly from public registry websites such as ClinicalTrials.gov, EuClinicalTrials.eu, ISRCTN.com, etc., and has not been edited.

Official Title:

A phase III, randomized, open-label study evaluating the efficacy and safety of giredestrant in combination with phesgo versus phesgo after induction therapy with phesgo + taxane in patients with previously untreated HER2-positive, estrogen receptor-positive locally-advanced or metastatic breast cancer

Trial Summary:

This Phase III, randomized, two-arm, open-label, multicenter study will evaluate the efficacy and safety of giredestrant plus Phesgo compared with Phesgo after induction therapy with Phesgo plus taxane in participants with human epidermal growth factor receptor 2 (HER2)-positive, estrogen receptor (ER)-positive advanced breast cancer (metastatic or locally advanced disease not amenable to curative treatment) who have not previously received a systemic non-hormonal anti-cancer therapy in the advanced setting.

Hoffmann-La Roche	Phase 3
Sponsor	Phase

NCT05296798 2022-500014-26-00 WO43571
Trial Identifiers

Eligibility Criteria:

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Gender	Age	Healthy Volunteers
All	#18 Years	No

1. Why is the heredERA clinical trial needed?

Breast cancer is a disease in which cancer cells form in the breast tissue. Breast cancer can sometimes be diagnosed as “locally advanced unresectable” (the cancer has grown outside of the breast area, is not removable by surgery but has not yet spread to other parts of the body) or “metastatic” (the cancer has spread to other parts of the body). More effective treatments are needed for breast cancer that becomes locally advanced or metastatic.

Breast cancer cells can be positive for markers called ‘HER2’ and ‘ER’. The standard first treatment for people with locally advanced unresectable or metastatic breast cancer that is positive for HER2 and ER, is pertuzumab and trastuzumab (P + T) plus around six rounds of chemotherapy (with docetaxel or paclitaxel) – known as ‘induction therapy’. The aim of induction therapy is to destroy as many cancer cells as possible. Induction therapy is followed by regular P + T treatment with or without hormone therapy (such as tamoxifen or letrozole) to prevent or slow the growth of cancer cells – known as ‘maintenance therapy’. P + T therapy can be given as infusions (into a vein) or combined as a single injection (under the skin).

Adding a drug to maintenance therapy called giredestrant – which slows the growth of ER-positive cancer cells - may improve health outcomes for people with HER2-positive and ER-positive breast cancer. Giredestrant is an experimental drug – which means health authorities have not approved it for treating breast cancer. This clinical trial aims to compare the effects, good or bad, of giredestrant with combined P + T versus combined P + T with or without hormone therapy in people with locally advanced or metastatic HER2-positive, ER-positive breast cancer.

2. How does the heredERA clinical trial work?

This clinical trial is recruiting people who have locally advanced unresectable or metastatic HER2-positive, ER-positive breast cancer. People can take part if they have not yet been treated for advanced or metastatic disease. People who take part in this clinical trial (participants) will be given the clinical trial treatment P + T and either docetaxel or paclitaxel as standard induction therapy, followed by maintenance therapy with giredestrant and P + T or standard maintenance therapy (P + T with or without hormone therapy) for as long as it can help them. The clinical trial doctor will see them every 3 weeks. These hospital visits will include checks to see how the participant responds to the treatment and any side effects they may have. After the last dose of treatment, participants will visit the clinic one month later, then every 3 months for as long as they agree to it. The total time of participation in the clinical trial will depend on how the participant responds

to treatment, and could be up to about 7 years. Participants can stop trial treatment and leave the clinical trial at any time.

3. What are the main endpoints of the heredERA clinical trial?

The main clinical trial endpoint (the main result measured to see if the drug has worked) is the length of time between the start of maintenance therapy and participants' cancer getting worse (progression-free survival).

The other clinical trial endpoints include:

- How long participants live (overall survival)
- The number of participants whose tumours get smaller (objective response rate) and the amount of time this lasts if disease then progresses (duration of response)
- The number of participants who have tumours that disappear, get smaller, or stay the same size for at least 6 months (clinical benefit rate)
- Change from the start of treatment in participants' ability to do daily activities and quality of life
- The number and seriousness of any side effects

4. Who can take part in this clinical trial?

People can take part in this trial if they are at least 18 years old and have been diagnosed with HER2-positive, ER-positive breast cancer that is either locally advanced unresectable or metastatic. People may not be able to take part in this trial if they have certain other medical conditions such as liver or heart disease or uncontrolled infections, they have previously received certain treatments such as fulvestrant, are pregnant or breastfeeding, or are planning to become pregnant shortly after the clinical trial.

5. What treatment will participants be given in this clinical trial?

This is an open-label trial, which means everyone involved, including the participant and the clinical trial doctor, will know the clinical trial treatment the participant has been given. Treatment will be given in 3-week 'cycles' - a treatment cycle is the period of treatment and recovery time before the next dose of treatment is given.

Firstly, all participants will be given 4–8 cycles (depending on how they respond to treatment) of standard induction therapy in the 'induction phase' of the trial, as follows:

- P + T, as a single injection (under the skin) every 3 weeks, and
- Docetaxel or paclitaxel, as an infusion (into the vein)

Next, maintenance therapy will be given during the 'maintenance phase' of the trial. Maintenance therapy will be given until the participants' disease gets worse, they have unacceptable side effects, the trial ends, or they decide to leave the trial. Participants

will be split into two groups randomly (like flipping a coin), with an equal chance of being placed in either group, and given either:

- P + T, as a single injection (under the skin) every 3 weeks, and giredestrant, as a capsule to be swallowed once every day for as long as it can help
- OR P + T, as a single injection (under the skin) every 3 weeks, with or without hormone therapy as a capsule to be swallowed once every day for as long as it can help

Women who have not completed menopause and men will also be given an 'LHRH-agonist therapy', which is a standard treatment to lower natural levels of oestrogen, if they are given giredestrant or hormone therapy.

6. Are there any risks or benefits in taking part in this clinical trial?

The safety or effectiveness of the experimental treatment or use may not be fully known at the time of the trial. Most trials involve some risks to the participant. However, it may not be greater than the risks related to routine medical care or the natural progression of the health condition. People who would like to participate will be told about any risks and benefits of taking part in the clinical trial, as well as any additional procedures, tests, or assessments they will be asked to undergo. All of these will be described in an informed consent document (a document that provides people with the information they need to decide to volunteer for the clinical trial).

Risks associated with the clinical trial drugs

Participants may have side effects (an unwanted effect of a drug or medical treatment) from the drugs used in this clinical trial. Side effects can be mild to severe, even life-threatening, and vary from person to person. Participants will be closely monitored during the clinical trial; safety assessments will be performed regularly. Participants will be told about the known side effects of giredestrant and combined P + T and possible side effects based on human and laboratory studies or knowledge of similar drugs. Participants will be told about any known side effects of swallowing capsules, injections under the skin (subcutaneous injections), and infusions into a vein (intravenous infusions).

Potential benefits associated with the clinical trial

Participants' health may or may not improve from participation in the clinical trial. Still, the information collected may help other people with similar medical conditions in the future.

Inclusion Criteria:

- Histologically or cytologically confirmed and documented human epidermal growth factor receptor 2 (HER2)-positive/estrogen receptor (ER)-positive adenocarcinoma of the breast with metastatic or locally-advanced disease not amenable to curative resection

- At least one measurable lesion and/or non-measurable disease evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Disease-free interval from completion of adjuvant or neoadjuvant systemic non-hormonal treatment to recurrence of #6 months
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1
- Left ventricular ejection fraction (LVEF) of at least (#)50% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
- Adequate hematologic and end-organ function
- For women of childbearing potential: Participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agree to refrain from donating eggs, during the treatment period and for 7 months after the final dose of Phesgo
- For men: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, during the treatment period and for 7 months after the final dose of Phesgo to avoid exposing the embryo

Maintenance Phase Inclusion Criteria

- Complete a minimum of four cycles to a maximum of eight cycles of induction therapy; the minimum cycles are defined as either: Phesgo injections + 4 docetaxel infusions, or Phesgo injections + 12 paclitaxel infusions
- Achieve a minimum of stable disease (SD) (or Non-complete response [CR]/Non-progressive disease [PD] for participants with non-measurable disease) (i.e., did not experience PD) according to RECIST v1.1 at the last tumor assessment during the induction therapy phase
- LVEF of #50% at the last assessment during the induction therapy phase

Exclusion Criteria:

- Previous systemic non-hormonal anti-cancer therapy in the metastatic breast cancer (MBC) or advanced breast cancer (ABC) setting. Note: Up to one line of single-agent endocrine therapy given in the metastatic or locally advanced setting will be allowed.
- Prior treatment with a selective estrogen receptor degrader (SERD)
- Previous treatment with approved or investigative anti-HER2 agents in any breast cancer treatment setting, except Phesgo (or trastuzumab SC with pertuzumab IV, or pertuzumab and trastuzumab IV), single-agent trastuzumab IV or SC, ado-trastuzumab emtansine, lapatinib, and neratinib in the neoadjuvant or adjuvant setting
- Disease progression within 6 months of receiving adjuvant anti-HER2 therapy (such as trastuzumab, with or without pertuzumab [IV, SC, or fixed-dose combination], or ado-trastuzumab emtansine, or neratinib)
- Non-resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) Grade 1 or better
- History of persistent Grade #2 (NCI-CTC, Version 5.0) hematological toxicity resulting from previous adjuvant or neo-adjuvant therapy
- History of exposure to the following cumulative doses of anthracyclines; Doxorubicin >360 mg/m2; Liposomal doxorubicin >500 mg/m2; Epirubucin >720 mg/m2; Mitoxantrone >120 mg/m2; Idarubicin >90 mg/m2.
- Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease
- Dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 7 months after the final dose of Phesgo (Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of induction therapy).
- Treated with investigational therapy within 28 days prior to initiation of induction therapy
- Treated with localized palliative radiotherapy within 14 days prior to initiation of induction therapy
- Concurrent participation in any other therapeutic clinical trial
- Known hypersensitivity to any of the study medications or to excipients of recombinant human or humanized antibodies
- Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose of 10 mg/day methylprednisolone or equivalent)
- Poorly controlled hypertension
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, active liver disease including active viral or other hepatitis virus, autoimmune hepatic disorders, or sclerosing cholangitis, current alcohol abuse, or cirrhosis
- Active cardiac disease or history of cardiac dysfunction
- Major surgical procedure or significant traumatic injury within 14 days prior to enrollment or anticipation of need for major surgery during induction therapy
- Active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or major upper gastrointestinal surgery
- Concurrent, serious, uncontrolled infections, or known infection with HIV with the following exception: Individuals who are HIV positive are eligible provided they are stable on anti-retroviral therapy for #4 weeks, have a CD4 count #350 cells/uL, and have an undetectable viral load and no history of AIDS-defining opportunistic infections within 12 months prior to enrollment.
- Serious COVID-19 infection within 14 days prior to enrollment; however, no screening testing for SARS-CoV-2 is required
- Serious infection requiring oral or IV antibiotics within 7 days prior to screening
- Any serious medical condition or abnormality in clinical laboratory tests that precludes an individual's safe participation in the study
- History of malignancy within 5 years prior to screening with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death
- For pre- and perimenopausal women, and men: Known hypersensitivity to luteinizing hormone-releasing hormone agonist (LHRHa); Not willing to undergo and maintain treatment with approved LHRHa therapy for the duration of endocrine therapy that requires gonadal function suppression
- Treatment with strong CYP3A4 inhibitors or inducers within 14 days or 5 drug-elimination half-lives, whichever is longer, prior to initiation of giredestrant treatment in Arm B
- A documented history of hemorrhagic diathesis, coagulopathy, or thromboembolism, including deep vein thrombosis, unless the condition is adequately treated and under control