ForPatients
by Roche

Breast CancerInoperable Breast CancerBreast Cancer Er-PositiveLocally Advanced or Metastatic Breast Cancer

A study to look at how safe new treatment combinations are and how well they work for people with breast cancer that has spread to nearby tissues and cannot be removed with surgery, or has spread in the body

A Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Participants With Breast Cancer

Trial Status	Trial Runs In	Trial Identifier
Recruiting	5 Countries	NCT04802759 2020-004889-19 2023-507495-48-00 CO42867

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 Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Patients With Breast Cancer (MORPHEUS-BREAST CANCER)

Trial Summary:

This is a Phase Ib/II, open-label, multicenter, randomized umbrella study in participants with breast cancer. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population. Cohort 1 will focus on participants with inoperable, locally advanced or metastatic, estrogen receptor-positive (ER+), HER2-negative breast cancer who had disease progression during or following treatment with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i; e.g., palbociclib, ribociclib, abemaciclib) in the first- or second-line setting. Cohort 2 will focus on inoperable, locally advanced or metastatic, ER+, HER2-positive breast cancer with previous progression to standard-of-care anti-HER2 therapies, of which one was a trastuzumab-and-taxane-based systemic therapy (including in the early setting if recurrence occurred within 6 months of finishing adjuvant therapy) and one was a HER2-targeting antibody-drug conjugate (ADC; e.g., ado-trastuzumab emtansine or trastuzumab-deruxtecan) or a HER2-targeting tyrosine kinase inhibitor (TKI; e.g., tucatinib, lapatinib, pyrotinib or neratinib). Cohort 3 will focus on inoperable, locally advanced or metastatic, ER+, HER2-negative, PIK3CA-mutated breast cancer with resistance to adjuvant endocrine therapy.

Hoffmann-La Roche **Phase 1/Phase 2**

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Sponsor	Phase

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Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
Female	**#18 Years**	**No**

1. Why is this study needed?

Breast cancer is a health condition where cancer cells form in the breast. Breast cancer can be challenging to treat if it has spread to nearby tissues and cannot be removed with surgery (known as ‘locally advanced unresectable breast cancer’) or if it has spread to other parts of the body (known as ‘metastatic breast cancer’). Standard treatment includes chemotherapy (such as capecitabine, nab-paclitaxel and carboplatin) and/or hormone or targeted treatments. Treatment depends on the type of breast cancer a person has. New treatment combinations are needed to improve health outcomes for people with locally advanced unresectable or metastatic breast cancer.

This study is testing new targeted treatment combinations. They are experimental medicines. This means health authorities (like the U.S. Food and Drug Administration and European Medicines Agency) have not approved the new targeted treatment combinations for treating breast cancer.

This study aims to see how well new treatment combinations work in people with locally advanced unresectable or metastatic breast cancer, and how safe they are.

2. Who can take part in the study?

Females of at least 18 years of age with locally advanced unresectable or metastatic breast cancer can take part in the study if they meet certain criteria to join a particular treatment group, including the type of breast cancer they have and which treatments they have been given before, if any.

People may not be able to take part in this study if they have cancer that has spread to the brain or spinal cord and causes symptoms, certain medical conditions such as heart or lung diseases or certain infections, or have had severe reactions to previous cancer treatment. People who are pregnant, or currently breastfeeding cannot take part in the study.

3. How does this study work?

Participants will be screened to check if they are able to participate in the study. The screening period will take place from 1 month before the start of treatment.

Everyone who joins this study will be placed into a group (known as a ‘cohort’) that they fit the criteria for. The cohort will depend on the participant’s breast cancer type and any treatments they have received before.

More than 1 experimental treatment combination may be available to a cohort. In these cases, the cohort will be further split into treatment groups, with each group given a different study treatment. The chance of being given a certain study treatment will depend on the number of different treatments available to the cohort, and on the number of participants already in each treatment group.

Treatments will be given as combinations of pills (to be swallowed), injections under the skin, or drips into a vein (infusions) in treatment cycles. A treatment cycle is the period of treatment and recovery time before the next set of treatment is given – a cycle is usually 3 or 4 weeks.

This is an open-label study. This means everyone involved, including the participant and the study doctor, will know the study treatment the participant has been given.

During this study, the study doctor will see participants regularly. They will see how well the treatment is working and any unwanted effects participants may have. Study treatment will be given for as long as it can help, unless participants have unmanageable unwanted effects. Participants who have cancer that gets worse or who have unmanageable and unwanted effects while they are being given a particular study treatment, may be able to be given a different treatment in this study if they meet the criteria.

Participants will have follow-up visits, telephone calls or medical record checks every 3 months after completing the study treatment for as long as they agree to it, during which study doctor will check on the participant’s wellbeing. Total time of participation in the study could be up to 7 years, depending on when a person joins the study. Participants have the right to stop study treatment and leave the study at any time, if they wish to do so.

4. What are the main results measured in this study?

The main result measured to assess if the study treatments have worked is the number of participants who have a positive response to treatment.

Other key results measured in the study include:

- How long participants live without their cancer getting worse

- The number of participants whose tumours do not grow or shrink for at least 3 months after receiving study treatment
- The number of participants whose tumours shrink or stay the same for at least 6 months with study treatment
- How long participants live
- How much time there is between participants' cancer first responding to treatment and the cancer getting worse
- The number and seriousness of unwanted effects
- How the study treatment gets to different parts of the body, how the body changes and gets rid of it

5. Are there any risks or benefits in taking part in this study?

Taking part in the study may or may not make participants feel better. But the information collected in the study can help other people with similar health conditions in the future.

It may not be fully known at the time of the study how safe and how well the study treatment works. The study involves some risks to the participant. But these risks are generally not greater than those related to routine medical care or the natural progression of the health condition. People interested in taking part will be informed about the risks and benefits, as well as any additional procedures or tests they may need to undergo. All details of the study will be described in an informed consent document. This includes information about possible effects and other options of treatment.

Risks associated with the study treatment combinations Participants may have unwanted effects of the treatment combinations used in this study. These unwanted effects can be mild to severe, even life-threatening, and vary from person to person. During this study, participants will have regular check-ups to see if there are any unwanted effects.

Participants will be told about the known unwanted effects of the study treatments and possible unwanted effects based on human and laboratory studies or knowledge of similar medicines. Known unwanted effects include frequent watery stools, and wanting to throw up.

The study treatments will be given as combinations of pills (to be swallowed), injections under the skin, or infusions (into the vein). Known unwanted effects of injections under the skin include redness, swelling or rash on the skin where it has been pricked with a needle to give a treatment. Known unwanted effects of infusions include throwing up, wanting to throw up, a feeling of coldness that makes the body shiver, low or high blood pressure, fever, pain or discomfort in the head, frequent watery stools, shortness of breath, and cough.

The study treatments may be harmful to an unborn baby. Women must take precautions to avoid exposing an unborn baby to the study treatment.

Inclusion Criteria:

Inclusion Criteria for Cohort 1 (Stage 1 [and Stage 2, only where indicated]):

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Documented estrogen receptor-positive (ER+) tumor
- Patients for whom endocrine therapy is recommended and treatment with cytotoxic chemotherapy is not indicated at time of entry into the study, as per national or local treatment guidelines
- Radiologic/objective evidence of recurrence or progression after the most recent systemic therapy for breast cancer
- Disease progression during or after first- or second-line hormonal therapy for locally advanced or metastatic disease (note: at least one line of therapy must have contained a CDK4/6i administered for a minimum of 8 weeks prior to disease progression.)
- Postmenopausal status for women
- Life expectancy #3 months
- Availability of a representative tumor specimen that is suitable for biomarker evaluation via central testing
- Prior fulvestrant therapy is allowed
- Stages 1 and 2: Measurable disease (at least one target lesion) according to RECIST v1.1
- Stages 1 and 2: Adequate hematologic and end-organ function
- Stages 1 and 2: Stable anticoagulant regimen for patients receiving therapeutic anticoagulation

Inclusion Criteria for Cohort 2 (Stage 1 [and Stage 2, only where indicated]):

- ECOG Performance Status of 0 or 1
- Histologically or cytologically confirmed and documented adenocarcinoma of the breast with metastatic or locally advanced disease not amenable to curative resection
- ER+, HER2-positive breast cancer
- Postmenopausal status for women
- Life expectancy #3 months
- Willingness to have a representative tumor specimen that is suitable for biomarker evaluation via central testing submitted, if available
- Prior endocrine therapy in the advanced setting allowed, including fulvestrant if given more than 28 days prior to randomization, but excluding other selective estrogen receptor degraders (SERDs)
- Stages 1 and 2: Measurable disease (at least one target lesion) according to RECIST v1.1
- Stages 1 and 2: Baseline left ventricular ejection fraction (LVEF) #50% as measured by ECHO or MUGA scans
- Stages 1 and 2: Adequate hematologic and end-organ function
- Stages 1 and 2: Stable anticoagulant regimen for patients receiving therapeutic anticoagulation

Inclusion Criteria for Cohorts 1 and 2 (Stage 2):

- Ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity, disease progression as determined by the investigator according to RECIST v1.1, or loss of clinical benefit as determined by the investigator, provided that a Stage 2 slot is available and patient meets eligibility criteria for Stage 2
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 because of unacceptable toxicity to drugs, disease progression as determined by the investigator according to RECIST v1.1, or loss of clinical benefit as determined by the investigator

Inclusion Criteria for Cohort 3:

- Measurable disease (at least one target lesion) according to RECIST v1.1
- ECOG Performance Status of 0 or 1
- Documented ER+ tumor
- Patients for whom endocrine therapy is recommended and treatment with cytotoxic chemotherapy is not indicated at time of entry into the study, as per national or local treatment guidelines
- Histologically or cytologically confirmed and documented adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to surgical or radiation therapy with curative intent
- Patients must have progressed during adjuvant endocrine treatment or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen. If a CDK4/6i was included as part of neoadjuvant or adjuvant therapy, progression event must be >12 months since completion of CDK4/6i portion of neoadjuvant or adjuvant therapy.
- Postmenopausal status for women (including women on or starting luteinizing hormone-releasing hormone [LHRH] agonist for ovarian suppression prior to randomization)
- Life expectancy #6 months
- Adequate hematologic and end-organ function
- Confirmation of PIK3CA mutation status based on pre-existing test results (i.e., obtained as part of clinical practice) from blood or tumor tissue. If pre-existing test results are not available, submission of a freshly collected pretreatment blood sample for PIK3CA mutation status at a central testing site with the FoundationOne Liquid® CDx assay is required, outside of the E.U. In the E.U., only pre-existing test results are acceptable (central testing will not be provided).

Exclusion Criteria:

General Exclusion Criteria for all Treatment Arms in Stage 1, Cohorts 1 and 2 (unless only applicable to one cohort, as indicated):

- Prior treatment with any of the protocol-specified study treatments
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Systemic treatment for breast cancer within 2 weeks of Cycle 1, Day 1 or 5 half-lives of the drug prior to Cycle 1, Day 1
- Treatment with strong CYP3A4 inhibitors or inducers within 14 days or 5 drug elimination half-lives (whichever is longer) prior to randomization
- Adverse events from prior anti-cancer therapy that have not resolved to Grade #1 or better, with the exception of alopecia of any grade and Grade #2 peripheral neuropathy
- Eligible only for the control arm
- Prior allogeneic stem cell or solid organ transplantation
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study
- History of malignancy other than breast cancer within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures
- Uncontrolled tumor-related pain
- Uncontrolled or symptomatic hypercalcemia
- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases
- History of leptomeningeal disease
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
- History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan
- Active cardiac disease or history of cardiac dysfunction

- Positive HIV test at screening or at any time prior to screening
- Active Hepatitis B or Hepatitis C virus infection
- Active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or major upper gastrointestinal (GI) surgery, including gastric resection, potentially affecting enteral absorption
- Known allergy or hypersensitivity to any of the study drugs or any of their excipients
- Cohort 1 only: Known HER2-positive breast cancer
- Cohort 1 only: Concurrent hormone replacement therapy
- Cohort 1 only: Prior treatment with cytotoxic chemotherapy for metastatic breast cancer (with the exception of single agent capecitabine, which will count as a single line of therapy)
- Cohort 2 only: Dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
- Cohort 2 only: Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose of 10 mg/day methylprednisolone equivalent), excluding inhaled steroids

Additional Exclusion Criteria for Giredestrant + Abemaciclib Arm and Giredestrant + Abemaciclib + Atezolizumab Arm (Cohort 1, Stage 1):

- Interstitial lung disease or severe dyspnea at rest or requiring oxygen therapy
- History of major surgical resection involving the stomach or small bowel, or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea
- History of syncope of cardiovascular etiology, ventricular arrhythmia, or sudden cardiac arrest

Additional Exclusion Criteria for Giredestrant + Ipatasertib Arm (Cohort 1, Stage 1):

- Prior treatment with an Akt inhibitor
- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications
- Grade #2 uncontrolled or untreated hypercholesterolemia or hypertriglyceremia
- History of Type 1 or Type 2 diabetes mellitus requiring insulin
- History or presence of an abnormal electrocardiogram (ECG) that is clinically significant in the investigator's opinion

Additional Exclusion Criteria for Giredestrant + Inavolisib Arm (Cohort 1, Stage 1):

- Prior treatment with any PI3K, Akt, or mTOR inhibitor, or any agent whose mechanism of action is to inhibit the PI3K/Akt/mTOR pathway
- Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes
- Fasting glucose #126 mg/dL or #7.0 mmol/L and HbA1c #5.7%
- Any concurrent ocular or intraocular condition that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
- Active inflammatory or infectious conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye
- Symptomatic active lung disease, including pneumonitis
- Inability to confirm biomarker eligibility based on valid results from either central testing of blood or local testing of blood or tumor tissue that documents one of the protocol-defined PIK3CA mutations

Additional Exclusion Criteria for Giredestrant + Ribociclib Arm (Cohort 1, Stage 1):

- Currently receiving or has received systemic corticosteroids #2 weeks prior to starting trial treatment
- Impairment of GI function or GI disease that may significantly alter the absorption of the oral trial treatments

Additional Exclusion Criteria for Giredestrant + Samuraciclib Arm (Cohort 1, Stage 1):

- Prior treatment with mTOR inhibitor
- Receipt of systemic corticosteroids (at a dose >10 mg prednisone/day or equivalent) within 14 days before the first dose of samuraciclib
- Active bleeding diatheses
- History of hemolytic anemia or marrow aplasia
- Receipt of a live-virus vaccination within 28 days or less of planned treatment start

Additional Exclusion Criteria for Giredestrant + Atezolizumab-Containing Arms (Cohort 1, Stage 1):

- Active or history of autoimmune disease or immune deficiency
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Treatment with systemic immunostimulatory agents within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Pregnant or breastfeeding, or intending to become pregnant during study treatment or within 5 months for atezolizumab

Additional Exclusion Criteria for Giredestrant + PH FDC SC + Abemaciclib Arm (Cohort 2, Stage 1):

- Interstitial lung disease or severe dyspnea
- History of major surgical resection involving the stomach or small bowel, preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea, or a condition that may significantly alter the absorption of the oral trial treatments
- History of syncope of cardiovascular etiology, ventricular arrhythmia, or sudden cardiac arrest

Additional Exclusion Criteria for Giredestrant + PH FDC SC + Palbociclib Arm (Cohort 2, Stage 1):

- History of major surgical resection involving the stomach or small bowel, preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea, or a condition that may significantly alter the absorption of the oral trial treatments
- Interstitial lung disease or severe dyspnea

Exclusion Criteria for Cohort 3:

- Known HER2-positive breast cancer
- Prior treatment with any SERD (e.g., fulvestrant, novel oral), proteolysis targeting chimera, complete ER antagonist (CERAN), or novel SERM (other than tamoxifen, toremifene)

- Prior treatment with any PI3Kalpha (PIK3CA gene product), AKT or mTOR inhibitor
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Treatment with strong CYP3A4 inhibitors or inducers within 14 days or 5 drug elimination half-lives (whichever is longer) prior to randomization
- Adverse events from prior anti-cancer therapy that have not resolved to Grade #1 or better, with the exception of alopecia of any grade and Grade #2 peripheral neuropathy
- Major surgical procedure within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study
- History of malignancy other than breast cancer within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures
- Uncontrolled tumor-related pain
- Uncontrolled or symptomatic hypercalcemia
- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases
- History of leptomeningeal disease
- Severe infection within 4 weeks prior to initiation of study treatment
- Treatment for clinically significant infection with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
- History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan
- Active cardiac disease or history of cardiac dysfunction
- Positive HIV test at screening or at any time prior to screening
- Active Hepatitis B or Hepatitis C virus infection
- Active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or major upper gastrointestinal (GI) surgery, including gastric resection, potentially affecting enteral absorption
- Known allergy or hypersensitivity to any of the study drugs or any of their excipients