ForPatients
by Roche

Breast Cancer Er-PositiveBreast Cancer HER-2 NegativeBreast Cancer

A clinical trial to compare inavolisib plus fulvestrant versus alpelisib plus fulvestrant in people with hormone receptor-positive, HER2-negative, PIK3CA-mutated breast cancer that has spread during or after treatment with a CDK4/6 inhibitor plus hormone (endocrine) therapy

A Study Evaluating the Efficacy and Safety of Inavolisib Plus Fulvestrant Compared With Alpelisib Plus Fulvestrant in Participants With HR-Positive, HER2-Negative, PIK3CA Mutated, Locally Advanced or Metastatic Breast Cancer Post CDK4/6i and Endocrine Combination Therapy

Trial Status	Trial Runs In	Trial Identifier
Active, not recruiting	18 Countries	NCT05646862 2022-502322-41-00 WO43919

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, Multicenter, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Inavolisib Plus Fulvestrant Versus Alpelisib Plus Fulvestrant in Patients With Hormone Receptor-Positive, HER2-Negative, PIK3CA Mutated, Locally Advanced or Metastatic Breast Cancer Who Progressed During or After CDK4/6 Inhibitor and Endocrine Combination Therapy

Trial Summary:

This is a Phase III, multicenter, randomized, open-label, global study designed to evaluate the efficacy and safety of inavolisib plus fulvestrant compared with alpelisib plus fulvestrant in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) -negative, PIK3CA-mutated, locally advanced (LA) or metastatic breast cancer (mBC), who progressed during or after cyclin dependent kinase 4/6i (CDK4/6i)-based therapy.

Hoffmann-La Roche Sponsor	**Phase 3** Phase

NCT05646862 2022-502322-41-00 WO43919
Trial Identifiers

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Eligibility Criteria:

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

1. Why is the INAVO121 clinical trial needed?

The most common type of breast cancer is hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer. HR-positive, HER2-negative breast cancer can spread to nearby cells (known as ‘locally advanced’ cancer) or to other parts of the body (known as ‘metastatic’ cancer).

Standard treatment options for patients with HR-positive, HER2-negative metastatic breast cancer includes endocrine therapy, endocrine therapy combined with a type of drug called a CDK4/6 inhibitor, or chemotherapy. However, in most people with this type of breast cancer, the cancer eventually comes back (known as ‘relapse') because the treatments have stopped working.

Sometimes, cancer cells can have a changed version (also known as a ‘mutation’) of a gene called *PIK3CA*. Breast cancers with this type of mutation can relapse more quickly after standard treatment has been given.

Drugs such as inavolisib or alpelisib block the activity of this mutated *PIK3CA* gene to slow the growth of cancer cells and may be effective treatments after standard treatment stops working. Alpelisib, used with the endocrine treatment fulvestrant, is an approved treatment in some countries for patients with HR-positive, HER2-negative breast cancer with a *PIK3CA* mutation that has spread after standard endocrine therapy.

Inavolisib is an experimental treatment, which means health authorities have not approved it for the treatment of breast cancer or any other conditions. In this trial, researchers are looking at how well inavolisib works when given with fulvestrant compared with alpelisib plus fulvestrant, in people with HR-positive, HER2-negative breast cancer.

2. How does the INAVO121 clinical trial work?

This clinical trial is recruiting people who have a health condition called HR-positive, HER2-negative breast cancer that has a mutation in a gene called *PIK3CA*. People can take part if their cancer is locally advanced or metastatic and has not responded to previous treatment with a CDK4/6 inhibitor plus endocrine therapy.

The purpose of this clinical trial is to compare the effects, good or bad, of inavolisib plus fulvestrant versus alpelisib plus fulvestrant in people with HR-positive, HER2-negative,

PIK3CA-mutated breast cancer. People who take part in this clinical trial will receive either inavolisib plus fulvestrant or alpelisib plus fulvestrant.

Participants will be given the clinical trial treatment inavolisib plus fulvestrant OR alpelisib plus fulvestrant for as long as it can help them. Participants will be seen by the clinical trial doctor weekly during the first month of treatment and approximately once a month after that. These hospital visits will include checks to see how the participant is responding to the treatment and any side effects they may be having. After the final dose of the clinical trial treatment and the 30 days safety follow-up visit, the trial doctor will follow-up with participants by telephone or clinic visits approximately every 3 months for as long as they agree to it. Participants' total time in the clinical trial will depend on how their breast cancer responds to the clinical trial treatment and future follow-up treatments. This could range from 1 day to more than 7 years (including time on clinical trial treatment and time in follow-up). Participants are free to stop trial treatment and leave the clinical trial at any time.

3. What are the main endpoints of the INAVO121 clinical trial?

The main clinical trial endpoint (the main result that is measured in the trial to see if the treatment has worked) is how long participants live without their cancer getting worse (known as 'progression-free survival').

The other clinical trial endpoints are:

How long participants live (known as 'overall survival')

How many participants have a change in their tumour size or how much their cancer has progressed (known as 'overall response rate')

How much time passes between when participants' cancer first responds to treatment and when their cancer appears to get worse (known as 'duration of response')

The number of participants who respond to treatment (known as 'best overall response')

The number of participants who respond to treatment or have tumours that stay the same size for at least approximately 6 months (known as 'clinical benefit rate')

How much time passes from the start of the trial to when participants:

- feel less pain, or

- cancer appears to interfere less with their daily activities, or
- report an improved health-related 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 over 18 years old and have HR-positive, HER2-negative, *PIK3CA*-mutated breast cancer that has spread during or after treatment with a combination of a CDK4/6 inhibitor plus endocrine therapy.

People may not be able to take part in this trial if their cancer has spread to the brain or spinal cord and is untreated or is currently being treated. Or if they have certain other medical conditions, such as diabetes or an eye condition, that will require treatment during the trial. People may also be unable to take part in this trial if they have previously received certain treatments, if they are pregnant or breastfeeding or are planning to become pregnant.

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

Everyone who joins this clinical trial will be split into two groups randomly (like flipping a coin) and given either:

Group 1: inavolisib given as a single tablet (to be swallowed) once every day, and fulvestrant given as an injection into a muscle (intramuscular) once every two weeks during the first month, then once a month

OR

Group 2: alpelisib given as two tablets (to be swallowed) once every day, and fulvestrant given as an injection into a muscle (intramuscular) once every two weeks during the first month, then once a month

Participants will have an equal chance of being placed in either group.

This is an open-label trial, which means everyone involved, including the participants and the doctors, will know which clinical trial drugs each participant has been given.

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, although it may not be greater than the risks related to routine medical care or the natural progression of the health condition. Potential participants 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. These will all be described in an informed consent document (a document that provides people with the information they need to make a decision to volunteer for a clinical trial). A potential participant should also discuss these with members of the research team and with their usual healthcare provider. Anyone interested in taking part in a clinical trial should know as much as possible about the trial and feel comfortable asking the research team any questions about the 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 and even life-threatening and can vary from person to person.

Inavolisib, alpelisib and fulvestrant

Potential participants will be told about the known side effects of inavolisib, alpelisib and fulvestrant, and, where relevant, also potential side effects based on human and laboratory studies or knowledge of similar drugs.

Inavolisib and alpelisib will be given as oral tablets to be swallowed. Participants will be told about any known side effects of taking oral tablets.

Fulvestrant will be given by intramuscular injection, which will involve inserting a needle into a muscle of the upper buttocks. Participants will be told about any known side effects of intramuscular injection.

Potential benefits associated with the clinical trial

Participants' health may or may not improve from participation in the clinical trial, but the information that is collected may help other people who have a similar medical condition in the future.

For more information about this clinical trial see the **For Expert** tab on the specific ForPatients page or follow this link to ClinicalTrials.gov

Inclusion Criteria:

- If pre/perimenopausal women and men treatment with luteinizing hormone-releasing hormone (LHRH) agonist therapy beginning at least 2 weeks prior to Day 1 of Cycle 1
- Histologically or cytologically confirmed adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to surgical or radiation therapy with curative intent
- Documented HR +/ HER2- tumor according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines
- Confirmation of biomarker eligibility: detection of specified mutation(s) of PIK3CA via specified test
- Disease progression after or during treatment with a combination of CDK4/6i and endocrine therapy: <= 2 prior lines of systemic therapy in mBC setting; CDK4/6i based therapy does not need to be the last one received prior study entry; one line of chemotherapy in mBC setting allowed
- Measurable or evaluable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- Participants for whom endocrine-based 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
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Life expectancy of > 6 months
- Adequate hematologic and organ function prior to initiation of study treatment

Exclusion Criteria:

- Metaplastic breast cancer
- Prior treatment in locally advanced or metastatic setting with any PI3K, AKT, or mTOR inhibitor or any agent whose mechanism of action is to inhibit the PI3K/-AKT/-mTOR pathway
- Participant who relapsed with documented evidence of progression > 12 months from completion of adjuvant CDK4/6i based therapy with no treatment for metastatic disease
- Pregnant, lactating, or breastfeeding, or intending to become pregnant during the study or at least 60 days after the final dose of study treatment
- Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Any history of leptomeningeal disease or carcinomatous meningitis
- Known and untreated, or active central nervous system (CNS) metastases. Participants with a history of treated CNS metastases are eligible if they meet specific certain criteria
- Known active, systemic infection at study enrollment, or any major episode of infection requiring treatment with intravenous antibiotics or hospitalization within 7 days prior to Day 1 of Cycle 1
- 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
- Requirement for daily supplemental oxygen
- Symptomatic active lung disease, including pneumonitis
- History of or active inflammatory bowel disease
- Any active bowel inflammation
- Clinically significant and active liver disease, including severe liver impairment, viral or other hepatitis, current alcohol abuse, or cirrhosis
- Participants with known human immunodeficiency virus infection that meet specific criteria
- Investigational drug(s) within 4 weeks before randomization or within 5 half-lives of the investigational drug(s), whichever is longer

- History of other malignancy within 5 years prior to screening, except for cancers with very low risk of recurrence
- Chronic therapy of >= 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Allergy or hypersensitivity to components or excipients of the inavolisib, fulvestrant, or alpelisib formulations
- History of severe cutaneous reactions like Stevens-Johnson Syndrome, Erythema Multiforme, Toxic Epidermal Necrolysis, or Drug Reaction with Eosinphilia and Systemic Symptoms
- Active ongoing osteonecrosis of the jaw