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A study to assess the safety and effectiveness of inavolisib plus a cdk4/6 inhibitor and letrozole versus placebo plus a CDK4/6 inhibitor and letrozole in participants with advanced breast cancer

Submission date 10/01/2025	**Recruitment status** Recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 01/04/2025	**Overall study status** Ongoing	
Last Edited 14/01/2026	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims

The purpose of this study is to compare the effects, good or bad, of inavolisib plus palbociclib and letrozole versus placebo plus palbociclib and letrozole on patients with HR , HER2 advanced breast cancer. Participants in this study will get either inavolisib plus palbociclib and letrozole or placebo plus palbociclib and letrozole.

Inavolisib is a drug that works by blocking a signaling pathway that is used by cancer cells to grow, known as the PI3K pathway. A gene in this pathway, called PIK3CA, is sometimes mutated in breast cancer. Other studies have shown that inavolisib treatment may be more effective for patients whose breast cancer has mutated PIK3CA.

Who can participate?

This study will only enroll patients who have breast cancer with mutated PIK3CA.

What does the study involve?

Treatment will continue until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, death, or if the study is terminated by the Sponsor. The total duration of study treatment for each individual is expected to range from 1 day to more than 30 months.

Approximately 450 participants will be enrolled in this study.

Participants will be randomized to one of the following treatment arms in a 1:1 ratio:

Inavolisib plus palbociclib and letrozole

• Inavolisib: 9-mg tablet starting dose taken by mouth (PO) once a day (QD) continuously, on Days 1-28 of each 28-day cycle, beginning on Day 1 of Cycle 1

• Palbociclib: 125-mg capsule or tablet starting dose taken PO QD, ideally on Days 1 21 of each 28-day cycle, beginning on Day 1 of Cycle 1

• Letrozole: 2.5-mg tablet taken PO QD continuously

Placebo (for inavolisib) plus palbociclib and letrozole

• Placebo (for inavolisib): 9-mg tablet starting dose taken PO QD continuously, on Days 1-28 of each 28-day cycle, beginning on Day 1 of Cycle 1
• Palbociclib: 125-mg capsule or tablet starting dose taken PO QD, ideally on Days 1 21 of each 28-day cycle, beginning on Day 1 of Cycle 1
• Letrozole: 2.5-mg tablet taken PO QD continuously

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
There are risks, discomforts, and inconveniences associated with any research study. It is possible that these general risks could be increased by the addition of test medications. Some of the general risks may be potentially life threatening and may not have been previously reported.

Study Assessment Risks:
Some of these procedures take place more often than they would if patients were not taking part in this study.

Radiation Exposure Risks:
The ionising/radioactive radiation in this study has undergone CRE/MPE review.

Blood Collection:
Taking blood samples may cause bruising and discomfort and a risk of infection or blood clots at the site of the blood collection. If patients have a central line, this may be used for blood samples. There is always a risk of infection at the site where the line is fitted.

Study Treatment:
Inavolisib will be given in a clinic with emergency equipment and staff who are trained to monitor for and respond to any potential medical emergencies.

Risks Associated with Inavolisib:
Side effects can be referred to in the main PISICF due to the character count limit.

Unknown Risks:
It is possible that sides-effects of Inavolisib which are unknown at this time may occur during the study. Any new information that may affect participants' health or which may make the participants want to stop taking part in the study will be shared with them as soon as it becomes available.

Pregnancy Prevention:
There may be a risk in exposing an unborn child to study drugs, and all risks are not known at this time. Women must take precautions to avoid exposing an unborn child to study drugs, as described in the PIS-ICF.

Patients will be informed of all of the above risks in the Patient Information Sheet and will be asked to notify their study doctor or study staff should they experience any side effects during the study. Patients will be monitored throughout the study in order to minimise risks

Where is the study run from?
F. Hoffman La Roche (Germany)

When is the study starting and how long is it expected to run for?
January 2025 to August 2030

Who is funding the study?
F. Hoffman La Roche (USA)

Who is the main contact?
mania@gene.com

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-inavolisib-breast-cancer-spread-inavo-123

Contact information

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Integrated Research Application System (IRAS)
1010986

Central Portfolio Management System (CPMS)
64947

Protocol serial number
WO45654

Study information

Scientific Title
A phase III, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of inavolisib plus a CDK4/6 inhibitor and letrozole versus placebo plus a CDK4 /6 inhibitor and letrozole in patients with endocrine-sensitive PIK3CA mutated, hormone receptor-positive, HER2-negative advanced breast cancer

Study objectives
Primary objective:
To evaluate the efficacy of inavolisib plus a cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) and letrozole compared with placebo plus a CDK4/6i and letrozole with respect to time from randomization to the first occurrence of disease progression.

Secondary objectives:
1. To evaluate the efficacy of inavolisib plus a CDK4/6i and letrozole compared with placebo plus a CDK4/6i and letrozole with respect to time from randomization to death from any cause.
2. To evaluate the efficacy of inavolisib plus a CDK4/6i and letrozole compared with placebo plus a CDK4/6i and letrozole with respect to Investigator-assessed (confirmed ORR, DOR, CBR).
3. To evaluate patient-reported pain severity, functioning, and health-related quality of life (HRQoL) among participants treated with inavolisib plus a CDK4/6i and letrozole compared with placebo plus a CDK4/6i and letrozole.
4. To evaluate the safety of inavolisib plus a CDK4/6i and letrozole compared with placebo plus a CDK4/6i and letrozole.
5. To evaluate the tolerability of inavolisib plus a CDK4/6i and letrozole compared with placebo plus a CDK4/6i and letrozole from the participant's perspective.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Pending approval: 25/SW/0009

Primary study design
Interventional

Study design
Phase III multicenter randomized double-blind placebo-controlled study

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Endocrine-sensitive phosphatidylinositol 3-kinase (PIK3CA)-mutated, hormone receptor-positive, human epidermal growth factor receptor 2- (HER2-) negative advanced breast cancer

Interventions
Experimental Arm: Inavolisib + Letrozole + CDK4/6i

Treatment Summary: Participants will receive oral inavolisib once daily (QD), oral letrozole QD, and oral palbociclib on Days 1-21 of each 28-day cycle.
Total Duration of Treatment: Up to 7 years, depending on individual response and progression.
Follow-up: Participants will be followed up for up to 7 years to monitor outcomes and adverse events.

Placebo Comparator Arm: Placebo + Letrozole + CDK4/6i

Treatment Summary: Participants will receive oral placebo QD, oral letrozole QD, and oral palbociclib on Days 1-21 of each 28-day cycle.
Total Duration of Treatment: Up to 7 years, depending on individual response and progression.
Follow-up: Participants will be followed up for up to 7 years to monitor outcomes and adverse events.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Inavolisib, palbociclib, letrozole

Primary outcome(s)
Progression-Free Survival (PFS) from randomization to the first occurrence of disease progression or death from any cause, whichever occurs first (up to 7 years

Key secondary outcome(s)
1. Overall Survival (OS) is measured using death records from any cause at randomization and up to 7 years
2. Investigator-assessed Objective Response Rate (ORR) is measured at baseline and up to 7 years
3. Investigator-assessed Duration of Response (DOR) is measured from the first occurrence of a

confirmed objective response to the first occurrence of disease progression or death from any cause, whichever occurs first, up to 7 years
4. Investigator-assessed Clinical Benefit Rate (CBR) is measured at baseline and up to 7 years
5. Time to Confirmed Deterioration (TTCD) in Pain is measured from baseline until end of follow-up, up to 7 years
6. TTCD in Physical Function is measured from baseline until end of follow-up, up to 7 years
7. TTCD in Role Function is measured from baseline until end of follow-up, up to 7 years
8. TTCD in Global Health Status is measured from baseline until end of follow-up, up to 7 years
9. Percentage of Participants with Adverse Events is measured from baseline until end of follow-up, up to 7 years
10. Number of Participants Reporting Presence, Frequency, Severity, and/or Degree of Interference with Daily Function of Symptomatic Treatment Toxicities is measured using NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) at baseline and up to 7 years
11. Number of Participants Reporting Each Response Option for Treatment Side-effect Bother is measured using Question 5 (GP5) from the Functional Assessment of Cancer Therapy-General Questionnaire (FACT-G) at baseline and up to 7 years
12. Change from Baseline in Symptomatic Treatment Toxicities is measured using the PRO-CTCAE at baseline and up to 7 years
13. Change from Baseline in Treatment Side-effect Bother is measured using the FACT-G GP5 Item at baseline and up to 7 years

Completion date
31/08/2030

Eligibility

Key inclusion criteria
1. De-novo hormone receptor-positive (HR +) , HER2- advanced breast cancer (ABC), or, alternatively, relapsed HR + , HER2- ABC after at least 2 years of standard neoadjuvant/adjuvant endocrine therapy – If a CDK4/6i was included as part of that treatment, progression must not have occurred during or within 1 year of receipt of the CDK4/6i.
2. Confirmation of biomarker eligibility: valid results from either central testing of blood or pre-existing local testing of blood or tumor tissue documenting the presence of a study-eligible PIK3CA mutation.
3. Measurable disease per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1. 1).
4. Men or women of postmenopausal or premenopausal/perimenopausal status.
5. For men (and women of pre-/peri-menopausal status: willingness to undergo and maintain treatment with luteinizing hormone-releasing hormone (LHRH) agonist therapy for the duration of study treatment.
6. Adequate hematologic and organ function within 14 days prior to initiation of study treatment.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Any prior systemic therapy for locally advanced unresectable or metastatic breast cancer.
2. Appropriate for treatment with cytotoxic chemotherapy at time of entry into the study, as per national or local treatment guidelines (e.g., patients with visceral crisis).
3. Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes.
4. Inability or unwillingness to swallow pills.
5. Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control).
6. History of malignancy within 5 years prior to consent, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death.

Date of first enrolment
15/03/2025

Date of final enrolment
30/09/2027

Locations

Countries of recruitment
United Kingdom

England

Argentina

Australia

Brazil

Canada

China

France

Germany

Italy

Mexico

Poland

South Africa

Spain

Switzerland

Taiwan

Study participating centre
-
-
-
England
-

Sponsor information

Organisation
F. Hoffmann-La Roche Ltd

Funder(s)

Funder type
Industry

Funder Name
F. Hoffman La Roche

Results and Publications

Individual participant data (IPD) sharing plan
For eligible studies, qualified researchers may request access to individual patient level clinical data. See Roche's commitment to transparency of clinical study information here: https://go.roche.com/data_sharing

IPD sharing plan summary
Available on request