A phase III, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, high risk early breast cancer

Published: 29-08-2017
Last updated: 12-04-2024

To compare invasive disease-free survival (iDFS) for ribociclib + ET versus placebo + ET in patients with HR-positive, HER2-negative, EBCwith high risk of recurrence.

Ethical review	Approved WMO
Status	Pending
Health condition type	Breast neoplasms benign (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON45456

Source
ToetsingOnline

Brief title
CLEE011G2301 (EarLEE-1)

Condition

- Breast neoplasms benign (incl nipple)

Synonym
Breast Cancer, HER2

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Pharmaceutical company

Intervention

Keyword: Adjuvant Ribociclib with Endocrine Therapy in Hormone Receptor+/HER2-, High Risk Early Breast Cancer (EarLEE-1)

Outcome measures

Primary outcome

Invasive disease-free survival (iDFS) using STEEP criteria

Secondary outcome

- Recurrence-free survival (RFS) using STEEP criteria

- Distant disease-free survival (DDFS) using STEEP criteria

- Overall survival (OS)

- Quality of Life (QOL)

Study description

Background summary

While adjuvant endocrine therapy (ET) is effective in reducing risk of recurrence in patients with hormone receptor (HR)-positive early breast cancer (EBC), recurrences are still common, especially in patients with unfavorable clinical, pathological and/or molecular features. Ribociclib, a CDK4/6 inhibitor, demonstrated clinical efficacy with tolerable toxicity when added to ET in patients with HR-positive, HER2-negative advanced breast cancer.
The purpose of this study is to evaluate the effect of addition of ribociclib to standard adjuvant ET on invasive disease-free survival (iDFS) in patients with HRpositive, HER2-negative intermediate-risk EBC.

Study objective

To compare invasive disease-free survival (iDFS) for ribociclib + ET versus placebo + ET in patients with HR-positive, HER2-negative, EBC with high risk of recurrence.

Study design

This is a randomized, phase III, double-blind, placebo-controlled, multi-center, international study to evaluate efficacy and safety of ribociclib with ET as an adjuvant treatment in patients with HR-positive, HER2-negative high risk EBC.

Intervention

During Treatment phase ribociclib or ribociclib matching placebo will be given orally once a day on days 1-21 of each 28 day cycle. Days 22-28 of each cycle will be a *rest* period from ribociclib or placebo. Endocrine therapy (ET) will be given orally once a day on a continuous daily schedule (e.g., days 1-28 of each 28-day cycle).
GnRH agonist, per investigator*s judgement, (examples include but not limited to goserelin, triptorelin or leuprolide) will be given every 4 weeks for premenopausal women only. There will be no *rest* period in the ET schedule.

Study burden and risks

Based on preclinical and clinical data, treatment of ribociclib in combination with ET is expected to be tolerable and toxicities of the treatment are expected to be manageable and reversible upon dose reduction, treatment interruption or discontinuation.
Patients in this study will be carefully monitored for key toxicities that have been observed with ribociclib or endocrine treatments. Risk will be further minimized by adherence to inclusion/exclusion selection criteria, avoidance of prohibited medication, close safety monitoring and dose adjustment guidelines.

Contacts

Public
Novartis

Lichtstrasse 35
Basel 4056
CH
Scientific
Novartis

Lichtstrasse 35
Basel 4056
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Histologically confirmed unilateral primary invasive adenocarcinoma of the breast
* Estrogen receptor-positive and/or progesterone receptor-positive, HER2-negative breast cancer
* Patient is after surgical resection of the tumor where tumor was removed completely with the final surgical specimen microscopic margins free from tumor and with available archival tumor tissue from the surgical specimen
* Patient who have AJCC 8th edition Prognostic Stage Group III tumor; or patient who received neoadjuvant chemotherapy and have 1 or more ipsilateral axillary lymph nodes with residual tumor metastases greater than 2.0 mm in lymph node(-s) and residual tumor greater than 10.0 mm in breast tissue
• Patient has completed multi-agent adjuvant or neoadjuvant chemotherapy of >= 4 cycles or >= 12 weeks which included taxanes prior to screening
* Patient has completed adjuvant radiotherapy (if indicated) prior to screening
* Patient may already have initiated adjuvant endocrine therapy (ET) at the time of randomization, but randomization must take place within 52 weeks of date of initial histological diagnosis of breast cancer and within 12 weeks of initiating ET
* ECOG Performance Status 0 or 1
* Adequate bone marrow and organ function
* Sodium, potassium, phosphorus, magnesium and total calcium laboratory values within normal limits
* QTcF interval < 450 msec and mean resting heart rate 50-90 bpm ;Additional inclusion criteria as per full protocol may apply.

Exclusion criteria

* Prior treatment with CDK4/6 inhibitor
* Prior treatment with tamoxifen, raloxifen or aromatase inhibitors for reduction in risk (chemoprevention) of breast cancer and/or treatment for osteoporosis within last 2 years
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* Prior treatment with anthracyclines at cumulative doses of 450 mg/m² or more for doxorubicin or 900 mg/m² or more for epirubicin
* Distant metastases of breast cancer beyond regional lymph nodes
* Patient has not recovered from clinical and laboratory acute toxicities of chemotherapy, radiotherapy and surgery
* Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, or clinically significant cardiac arrhythmias
* Uncontrolled hypertension with systolic blood pressure >160 mmHg
* Patient is currently receiving any of the prohibited substances that cannot be discontinued 7 days prior to Cycle 1 Day 1: concomitant medications, herbal supplements, and/or fruits and their juices that are known as strong inhibitors or inducers of CYP3A4/5; medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5; systemic corticosteroids <= 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such
treatment; concomitant medications with a known risk to prolong the QT interval and/or known to cause torsades de points that cannot be discontinued or replaced by safe alternative medication.
* Pregnant or breast-feeding (lactating) women or women who plan to become pregnant or breast-feed during the study
* Women of child-bearing potential unless they are using highly effective methods of contraception during the study treatment and for 21 days after stopping the study treatment ;Additional exclusion criteria as per full protocol may apply.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2017
Enrollment:	55
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	anastrozole
Generic name:	NA
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	exemestane
Generic name:	NA
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	letrozole
Generic name:	NA
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	ribociclib
Generic name:	NA
Product type:	Medicine
Brand name:	tamoxifen
Generic name:	NA
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	29-08-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	07-12-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2014-001795-53-NL
ClinicalTrials.gov	NCT03078751
CCMO	NL61281.056.17