A phase II randomized, double-blind placebo controlled, study of letrozole with or without BYL719 or buparlisib, for the neoadjuvant treatment of postmenopausal women with hormone receptor-positive HER2-negative breast cancer (CBYL719A2201)

Published: 12-11-2013
Last updated: 24-04-2024

Primary objective: Determine whether treatment with a PI3K inhibitor (BYL719 or buparlisib) plus letrozole leads to an increase in pathologic response compared to treatment with placebo plus letrozole in patients with hormone receptor-positive HER2-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON45221

Source
ToetsingOnline

Brief title
CBYL719A2201 NEO-Belle/Neo-Orb

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer; HR+ HER2- breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis Pharma B.V.
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: breast cancer, BYL719, letrozole

Outcome measures

Primary outcome

pCR. and ORR based on tumor tissue

Secondary outcome

pCR and ORR based on cDNA, adverse events, breast conserving surgery, Ki67, PK

parameters.

Study description

Background summary

Letrozole is indicated for adjuvant and first line therapy for hormone receptor (HR)+ breast cancer (BC) patients and is considered a valid therapeutic option for neoadjuvant treatment of postmenopausal HR+ BC patients. While the introduction of adjuvant treatment of estrogen receptor (ER)+ postmenopausal breast cancer patients with hormonal therapy has led to improved long term outcomes, there remains a nonnegligible percentage of patients relapsing after standard adjuvant treatment with 5 years of letrozole (16%), justifying the need for more efficient treatments. Because efficacy of adjuvant treatment is based on long term outcomes, neoadjuvant testing offers a quick way to identify which combination may lead to a better outcome over a single agent endocrine treatment. Pathological complete response (pCR) is one of the indicators of response to neoadjuvant treatment and it has been shown to be linked to long term outcomes for neoadjuvant chemotherapy treatment in certain BC diseases.

However, pCR rate remains low with endocrine single agent. As a general concept, the inhibition of the PI3K-AKT-mTOR pathway has already been shown to lead to improved clinical outcomes when everolimus was added to letrozole. Promising pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy. Furthermore, clinical activity has been observed with single agent BYL719 or buparlisib in heavily pre-treated ER+ BC patients and when buparlisib was given in combination with letrozole to metastatic breast cancer patients.
The PI3K pathway might be activated via different routes. Within the given ER+/PR+ subtype, activation can be seen via PIK3CA mutations or PTEN alterations. Hence the use of an alpha-specific PI3K inhibitor like BYL719 or a pan-PI3K inhibitor like buparlisib in combination with letrozole may improve letrozole single agent outcomes by increasing the rate of tumor cell apoptosis. It is hypothesized that inhibiting the PI3K pathway upfront in combination with estrogen deprivation might be sufficient to lead to an increase in pathologic response and might prove to be an effective treatment in neoadjuvant treatment for postmenopausal HR+ HER2- BC patients.
In addition, in theory, an alpha specific inhibitor would demonstrate superior efficacy in the PIK3CA-mutant cancer population, with a potentially improved safety profile as compared to pan class I PI3K inhibitors. On the other hand, a pan PI3K inhibitor may offer benefit over an alpha specific one by being possibly active in circumstances where PI3K is activated via other subunits such as PTEN or INPP4B altered breast cancer.
However, there is lack of sufficient preclinical data to predict respective impact of alpha versus pan-PI3K inhibition in ER positive breast cancer in the clinic and only a trial using both compounds in the same patient population could provide additional preliminary information to help differentiate the compounds in this context.
The purpose of the study is to determine whether treatment with a PI3K inhibitor (BYL719 or buparlisib) plus letrozole leads to an increase in pathologic response compared to treatment with placebo plus letrozole in patients with hormone receptor-positive HER2-negative breast cancer for the following populations: i) in patients with tumors harboring a mutation in the PIK3CA gene ii) in patients with tumors harboring a wild type PIK3CA gene.
Update AM5:As part of a program-wide assessment of Buparlisib (BKM120) in breast cancer across different indications, and considering the modest efficacy observed in the Belle-2 study (Baselga, 2015), Novartis has decided not to pursue further the development of buparlisib in early-stage breast cancer. Ongoing patients receiving buparlisib/buparlisib-placebo and letrozole may continue the treatment based on the investigator*s clinical judgement. Patients recruited under buparlisib/buparlisib-placebo will still be part of the statistical analysis. However, the assessment of the anti-tumor activity of buparlisib/buparlisib-placebo plus letrozole will now become an exploratory objective.

Study objective

Primary objective: Determine whether treatment with a PI3K inhibitor (BYL719 or buparlisib) plus letrozole leads to an increase in pathologic response compared to treatment with placebo plus letrozole in patients with hormone receptor-positive HER2-negative breast cancer for the following populations: i) in patients with tumors harboring a mutation in the PIK3CA gene ii) in patients with tumors harboring a wild type PIK3CA gene based on tumor tissue.
Update AM5: assess the anti-tumor activity of BYL719 QD plus letrozole versus letrozole alone in increasing the Objective Response Rate (ORR) during neo-adjuvant treatment among postmenopausal patients with HR+, HER2-negative breast cancer for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild tumor types based on tumor tissue.
Secondary objective: pCR and ORR (complete + partial) based on cDNA, safety and tolerability, rate of breast conserving surgery, association between changes in Ki67 from baseline to day 15, and baseline to surgery, with pCR for each of the two cohorts, namely PIK3CA mutated and PIK3CA wild type, PEPI score in both cohorts, pharmacokinetics.

Study design

Double blind randomized phase II study. Approximately 360 patients (180 PIK3CA mutated and 180 wild type).
Randomization (1:1:1) to
* BYL 719 plus letrozole
* Placebo plus letrozole (50% placebo to BYL719, 50% placebo to buparlisib)
Neoadjuvant treatment for 24 weeks.
Follow-up for survival.

Intervention

Treatment with letrozole ± BYL719

Study burden and risks

Risk: Adverse events of study medication.
Burden:
4 visits during cycle 1, 2 during cycle 2 and 1 during cycles 3-6. Duration 2-3 h. If separate consent for participation to PK has been obtained: 2 visits of 9h duration and 2 extra visits.
Fasting blood tests during every visit (except day 1 cycle 1) 20-35 ml per occasion.
ECGs: day 1 of every cycle.
Echocardiography or MUGA-scan at screening and end of treatment.
Tumor evaluations after cycle 3 and 6.
Tumor biopsy at screening (in principle archived sample), during treatment and

at end of treatment (during surgery).
Diary about medication intake.
Follow-up for survival.

Contacts

Public
Novartis Pharma B.V.

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis Pharma B.V.

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Postmenopausal women (at time of breast cancer diagnosis) with HR+ HER2- breast cancer, Tc1-T3, M0 operable. See protocol page 49 for details.
* 18 years and above.
* Measurable disease.
* Biopsy available for the analysis of PIK3CA mutation and Ki67 level. Results known.
* ECOG performance status 0-1.

Exclusion criteria

* Recurrent or metastatic disease.
* Any systemic therapy or radiotherapy for current breast cancer.
* Patients with type 1 diabetes mellitus, or not adequatly type 2 diabetes mellitus.
* Left Ventricular Ejection Fraction < 50%.
* Currently receiving or has received systemic corticosteroids * 2 weeks prior to starting study drug.
* History of acute pancreatitis
* uncontroled hypertension

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-02-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BYL719
Generic name:	BYL719
Product type:	Medicine

Brand name:	Femara
Generic name:	Letrozole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-11-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-03-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-03-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-06-2014

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-07-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-10-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-06-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-07-2015

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-07-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-08-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-12-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-03-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-04-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-11-2016

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-01-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-02-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2013-001862-41-NL
ClinicalTrials.gov	NCT01923168
CCMO	NL46099.058.13